The Magic Molecule

that has improved the lives of millions

Börje Svensson
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Photo at the front page:
“White leghorn rooster” by Sándor Szirmai.
Gift from the artist to Endre Balazs (May 22, 1962)
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Preface

Millions of people all over the world are granted better vision thanks to a seemingly magic molecule. The molecule makes it possible to remove the eye’s lens and replace it with an artificial one. Cataracts are the cause of most lens replacements. The disease clouds the lens which in turn blurs vision. Until the early 1980’s, lens transplants were a very complicated affair, so much so that many eye surgeons avoided the procedure altogether. The revolutionary events that have taken place since, now allow surgeons to perform a lens transplant in less than 15 minutes, the results of which are successful nearly every single time. This medical breakthrough was made possible by the magic molecule described in this book.

The same molecule has also helped to ease ailing knees affected by arthritis. Despite the controversial nature of the molecule’s use in treating arthritis, the fact remains that many of the millions of people treated yearly report significant relief as a result. Furthermore, the molecule’s use in treating joints is not limited to those of humans, but also includes horses. Then working as product manager for the Swedish pharmaceutical company Pharmacia, I was personally involved in introducing Healonid® Vet., a product based on the magic molecule, into the French equestrian market some forty years ago.

As if eyes, knees and horses were not enough, the magic molecule has even revolutionized the global beauty industry during the past twenty years. Commonly used as the main ingredient in dermal fillers, the molecule has enabled many of the most successful wrinkle reducing products developed by world leading companies.

The magic molecule I speak of is a sugar molecule called hyaluronic acid. The modern term for the molecule is hyaluronan, often shortened HA. For the purposes of this book, the term hyaluronic acid will be used, since this is still the term most frequently used. Hyaluronic acid is found in a number of areas within the human body. In the human skin, hyaluronic acid works as a moisturizing and filling agent. In the human joint it acts as a lubricant and shock absorber. It is also found in the eye and the umbilical cord. Hyaluronic acid is also found in sources outside the human body. The hyaluronic acid described in this book originates from rooster combs or synthetically, through a process of bacterial fermentation.

Hyaluronic acid was discovered in 1934 by Karl Meyer and John Palmer, researchers at Columbia University. A Hungarian researcher by the name of Endre Balazs was the first to develop hyaluronic acid for commercial use. In 1943, Balazs received a patent for a method using fluid from knee joints of cows to be used as an egg white substitute in baking. The product itself was not very successful, but Balazs was inspired to search
for other commercial uses for hyaluronic acid. In particular, he was eager to discover medical benefits of its use. Endre Balazs is still driven by this eagerness, at 95 years of age. Throughout his career, he has successfully transformed research into practical benefit to an extent that most researchers only dream of.

Part I: The first six years (1971-77) – if not for the placebo effect

If it is possible to call a molecule magic, hyaluronic acid is certainly deserving. That which has been accomplished as a result of its discovery has been truly astounding. Hyaluronic acid’s commercial journey within medicine began some 43 years ago, marked by Endre Balazs crossing paths with Torvard Laurent, professor at Uppsala University, and Harry Hint, Chief Scientific Officer at Pharmacia, a pharmaceutical company located in Uppsala, Sweden. Both Laurent and Hint knew Balazs from his time as guest researcher at Karolinska Institutet (KI) in Stockholm in the late 1940’s.

The meeting between the three men began a chain of events as extraordinary as few others within the pharmaceutical industry. The endeavor began carefully, and even risked total collapse after only a few short years. The originally intended area of application for hyaluronic acid, or Healon®, as it was commercially called, proved to be unsuccessful. The details of such a conclusion are a matter of debate, but the fact remains that Pharmacia was unable to introduce Healon onto the market as first planned, thus endangering the entire operation. Healon was in fact released onto the French equestrian market, but the goal all along was to create an arthritis treatment for human knees. This was never realized. There was never any doubt as to the effectiveness of Healon on human patients, as many reported significant relief. However, there was also a high placebo effect during clinical trials which proved an insurmountable problem with regard to commercial release.

After Healon’s release onto the French equestrian market, I left Pharmacia in pursuit of an academic career. Interestingly, Healon would follow me on my new career path. Shortly after leaving Pharmacia, I found myself in the unique position of evaluating the very process with which I had been actively involved. When I delivered my analysis of the Healon project in December, 1977, few if any believed that the project could be salvaged. The first part of this book describes the period from Pharmacia’s initial collaboration with Endre Balazs in 1971 until the end of 1977.
Part II: Hyaluronic acid aids cataracts – the Healon project’s saving grace

During what could be described as the project’s darkest time, early 1978, a new use for hyaluronic acid was encountered, completely revitalizing the diminishing hopes at Pharmacia. Hyaluronic acid proved to be an invaluable aid in lens transplants in cataracts patients. The discovery revolutionized the surgery procedure almost overnight. Within a few years Healon had grown to become Pharmacia’s largest product.

Part II describes the discovery of this eye treatment and how the newly formed eye business division at Pharmacia succeeded in capitalizing on the commercial opportunities that arose. Success often comes with a price, and an outspoken research and development manager by the name of Bengt Ågerup would be abandoned by Pharmacia during the Healon adventure. Despite his departure, Ågerup would remain a vital actor in the development of hyaluronic acid, though not at Pharmacia. His return in the story told by this book begins already in Part III.

Part III: Biomatrix – a successful company born out of protest

Endre Balazs was certainly satisfied with having licensed a product to Pharmacia which became one of the global eye market’s largest selling products ever. Naturally, Healon’s success even meant large financial gains for him personally in the form of royalties. However, his satisfaction was carefully balanced with an equally large feeling of frustration with regard to Pharmacia’s disinterest in hyaluronic acid as an arthritis treatment. Balazs was convinced that Healon’s largest potential was to be found not within eye treatment, but rather on the arthritis market. Concerns surrounding the high reports of placebo effects were unfounded, according to Balazs. Tired of waiting for further development, Endre Balazs and his wife Janet Denlinger eventually took matters into their own hands, starting Biomatrix, Inc. The company was steered by Balazs and Denlinger from 1981 until 2000. Endre Balazs’ son André became General Manager and a member of the company’s board of directors. André Balazs would later have huge success within the hotel business. The main purpose of Biomatrix was to prove once and for all hyaluronic acid’s potential as a treatment for arthritic knees. To aid in achieving this goal, the company enlisted the help of former Pharmacia employee Bengt Ågerup. He eventually assumed the role of CEO for Biomatrix’ Swedish subsidiary. Ågerup’s involvement remained, even after eventually parting with Biomatrix. If hyaluronic acid could be described as the book’s leading actor, Balazs and Ågerup are the most important members of the supporting cast.

Endre Balazs managed to reach his goal. Biomatrix would eventually release Synvisc®, which became one of the leading products during the late 1990’s within arthritic knee
treatments. The company would also develop and introduce the world’s first hyaluronic acid-based injectable wrinkle filler. Hylaform®, as the product was called, was released onto the European cosmetics market in 1996. The prosperity realized primarily by Synvisc led to the sale of Biomatrix to the U.S. company Genzyme in year 2000. The selling price was 738 million US$. Part III tells the story of Biomatrix, a successful manifestation of frustration.

Part IV: Xalatan® – spin off product turned blockbuster

Part IV takes a bit of a detour, in that it describes a product that does not contain hyaluronic acid. The product, Xalatan®, is a so-called prostaglandin, used for treating glaucoma. It became the world’s first blockbuster product within eye medication. Yearly sales top one billion US$. Unfortunately for Pharmacia, Uppsala, and Sweden, the same year as Xalatan became a blockbuster, in 2003, the company was absorbed by American Pfizer.

Xalatan would have never been developed by Pharmacia if not for Hungarian researcher László Bitó being a good friend and colleague of Endre Balazs. The case of Xalatan is interesting for a number of reasons, not the least of which when compared to Healon. While Healon was driven forward by the passion of its inventor, Endre Balazs, who would eventually impose success by starting his own company after growing weary waiting for Pharmacia to act on the arthritis market, Lászsló Bitó displayed much the opposite approach in terms of Xalatan’s commercial achievements. Bitó was entirely uninterested in business, even being forced by his financiers to apply for a patent on that which would become Xalatan. Though Bitó was active during the product development phase, he quickly retreated once the product was released and his royalties began rolling in. Instead, Bitó took advantage of being able to pursue his lifelong dream as an author.

Part V: Hyaluronic acid's success as dermal filler – the result of a misunderstanding

New markets appear at times as the result of rather strange developments. The market for dermal fillers, (injected under the skin to smooth wrinkles or give volume to other parts of the face), is likely the only one to have come about as the result of a magazine article falsely claiming that hyaluronic acid could be found in cabbage. Part V describes the instance closer. Readers will also follow the close race between Biomatrix’ Hylaform and Q-Med’s Restylane® in being first out on the market with a hyaluronic acid-based dermal filler. The race itself took place unbeknownst to key
actors, with some players competing for more than one team simultaneously. Hylaform would eventually win, and after fading away left room for a number of new dermal fillers. A large number of the products developed in the wake of the dermal filler revolution could be traced directly to former Pharmacia R&D boss, Biomatrix contributor and founder of hyaluronic acid-based companies Bohus BioTech and Q-Med, Bengt Ågerup and his educator, Endre Balazs.

Part VI: Some final thoughts

The story of the magic molecule is one that describes a number of different stories, most of them success stories, and the different business, marketing and product development strategies involved. Also described are the dynamics between different individuals during the journey, from collaborative harmony to adversity and even deceit. The story raises a number of questions, both large and small, for example: What is required from a societal and business standpoint in order to develop and sell an internationally successful medical product? And: Is it possible to be successful in business while remaining reliable and honest?

Part VI focuses on two aspects I consider important from a business and innovation perspective, and for the discussion of which the book provides rich background material. These two aspects are:

- Management of conflict, and
- Factors for success

The first aspect is discussed on the basis of 16 different conflicts selected from an even larger number of conflicts presented in the book. The conflicts are analyzed with the help of the so-called TKI-model (Thomas-Kilman conflict model), a model frequently used in connection with conflict management.

The second aspect is discussed with the help of seven “Ps”. To the “famous four” of the marketing-mix model; Product, Price, Promotion and Place I have added People, Permission and Possession.

With this background information about the book, let’s go to the beginning of the story.
Part I: The early years of the Healon project (1971-77)

CHAPTER 1: Introduction

Horse treated with drug from rooster-comb wins gold for France

The Olympic summer games in Montreal in 1976 were on their way to complete failure for the great sporting nation of France. By the last day of competition the country had captured only one gold medal, thanks to Guy Drut on 110 m hurdles. Hopes of winning a second gold medal during the last day of the games, where the only remaining

1 Photo published at different Internet sites. Information about the picture received from Ecuries Sylvie Parot, Arbonne La Foret, France. Photographer unidentified.
competition was the equestrian team jumping, were low, particularly since one of the
best horses of the team, Rivage, had suffered from lameness shortly before the
departure from France. Luckily, initial fears proved to be unfounded. Rivage was in
excellent condition, the French team won its eagerly anticipated gold medal, and the
French honor was saved.

In connection with the annual congress of French veterinarians in October 1976, “the
miracle in Montreal” was explained. The person who summarized the events
surrounding Rivage’s recovery was French veterinarian Jean Plainfossé, who worked
for Hubert Parot, owner and rider of Rivage. When Rivage was diagnosed with joint
inflammation in July, 1976, Dr. Plainfossé opted to treat the horse with an injection of
Healon2. Largely unheard of at the time, the injectable substance was based on
hyaluronic acid extracted from rooster combs. It was being produced by the Swedish
pharmaceutical company Pharmacia on license from the U.S. company Biotrics, Inc.,
owned by Dr. Endre Balazs. Dr. Plainfossé had access to the drug through his role as
advisor to Pharmacia, and assisted the company in launching Healon on the French
veterinary market. The effect of the injection on Rivage was exceptional, Dr.
Plainfossé told his attentively listening colleagues. The horse rapidly recovered from
its injury and literally flew over the hurdles in Montreal.

This anecdote is significant for two reasons. First, it describes an important event in
Healon’s future success on the French racehorse market. Secondly, I happened to be at
the congress of French veterinarians in Paris in October 1976 in my role as product
manager for Healon. It was there I heard Dr. Plainfossé’s presentation of the “miracle
in Montreal”.

Actively participating in the launching of Healon on the French racehorse market was
a fantastic experience for a young man at the beginning of his career. It meant visits to
the renowned racecourses at Longchamps, Auteuil and Vincennes, combined with fine
dining at the best restaurants in Paris. It also meant visiting the training camp,
Grosbois, outside Paris, where my colleagues and I had the opportunity to talk about
trotting with legendary brothers Jean-René and Michel-Marcel Gougeon3. And yet, the
racehorse market was not our main professional interest. Rather it was a mere substitute
in anticipation of grander plans. But before explaining this further, let us go back in
time another couple of years in order to paint a clear picture of the purpose of this book.

2 Healon® was the brand name under which the product was to become known. However, at the
French market the product sold under the brand name Healonid® Vet.

3 Both brothers were multiple winners of Prix d’Amerique and Jean-René also, in 1978, was winner of
“Elitloppet” at the Swedish racecourse Solvalla, with Hadol du Vivier.
A meeting between three old friends

In August 1971, three old friends met at the home of Torvard Laurent in Uppsala, Sweden. Laurent was at the time professor in medical and physiological chemistry at Uppsala University, and his two guests were the researcher and inventor Endre Balazs, director of the Boston Biomedical Research Institute and owner of the company Biotics, Inc., and Harry Hint, Chief Scientific Officer at the pharmaceutical company Pharmacia in Uppsala. The three had known each other since the late 1940’s, when Balazs was a visiting researcher at the department of experimental histology at Karolinska Institutet (KI) in Stockholm, and Laurent and Hint were medical students there.

Endre Balazs had been recruited to KI in connection with his participation in “the Sixth International Congress of Experimental Cytology” in Stockholm in July 1947, where he gave a lecture entitled "The Influence of Extracellular Macromolecular Polysaccharides on the Development and Growth of Fibroblasts in Cultures”. A long and awkward title perhaps, but worth noting is that the lecture was about the glycosaminoglycan hyaluronic acid, a molecule on which Balazs had already spent eight years of his professional life. As this is being written (March, 2015), eight years has become almost 76. Endre Balazs is still, at 95 years of age, actively doing research on hyaluronic acid.

The lecture at the congress was well received and resulted in Balazs receiving a couple of offers from different Swedish research institutions, including one from Professor Hjalmari Holmgren at the department of experimental histology at KI. Balazs was working at the time as an assistant professor at the medical school at the University of Budapest, and was also involved in setting up a biology laboratory at the Museum of Natural History in Budapest. The possibilities of conducting research in Budapest at this time were limited due to the very unstable political situation. Balazs therefore decided to accept Holmgren’s invitation to work as a visiting researcher at his department. Balazs remained at KI from the autumn of 1947 until December, 1950, when he was invited to set up a new research institute associated with Harvard University and the Massachusetts Eye and Ear Infirmary in Boston. This was the start of the Retina Foundation, later to become Boston Biomedical Research Institute, where Endre Balazs would spend the next 25 years of his career.

Torvard Laurent and Endre Balazs became close associates at KI and co-authored four of the ten scientific reports that Balazs published during the period 1950-52. Laurent was a visiting researcher at the Retina Foundation in Boston on two occasions; 1953-54 and 1959-61. The title of his doctoral thesis, which was defended at Uppsala University in 1957, was “Psychochemical studies on hyaluronic acid”.

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The acquaintance between Endre Balazs and Harry Hint was linked to the advanced equipment for microcinematography that Balazs had built in his laboratory at KI, which Hint used for studies of the anticoagulant activity of dextran when injected into small blood vessels of animals. Dextran had been an important product area at Pharmacia since the late 1940’s, and the company was thus Hint’s first choice when looking for employment after having finished his studies in medicine.

Laurent and Balazs developed a close professional and personal relationship, both through Laurent’s two stints as visiting researcher at Retina Foundation, and through Balazs periods as visiting researcher at KI, the last of which lasting a little less than a year 1968-69. Endre Balazs also received an honorary doctorate degree at the Faculty of Medicine of Uppsala University in 1967. Torvard Laurent had continuous contact with Hint through various co-operation projects between his department at Uppsala University and Pharmacia. With regard to Balazs and Hint, the dinner at Laurent’s home in August 1971 was their first meeting since 1950.

The idea to meet at Laurent’s home was the result of a continuous dialogue between Balazs and Laurent. Balazs was convinced that there existed large therapeutic potential for hyaluronic acid in various fields of application. In 1968 he had started Biotrics, Inc. to try to exploit this potential. During prior years, negotiations with companies in the U.S. and Japan had proved fruitless. He and Laurent’s plan was to try to establish contact with Pharmacia’s top management through Harry Hint. The primary goal was to discuss the possibility of co-operating in Europe.

Balazs arrived at the meeting well prepared. He had compiled an extensive document entitled “Hyaluronic Acid and Matrix Implantation – a report on the Biological Activity and Therapeutic Use of Hyaluronic Acid,” which he gave to Hint. Hint listened attentively to Balazs’ and Laurent’s presentations of the key characteristics of hyaluronic acid, and his spontaneous assessment was that it could be of interest to Pharmacia both from a skills as well as a marketing perspective. But when Laurent and Balazs suggested that Hint pass on the information to top management of Pharmacia, he objected.

In order to start a new project at Pharmacia, it was first necessary to convince then CEO, Gösta Virding. If Hint presented the project there was risk that Virding would turn it down. Hint was convinced that the idea would be better received if delivered by a trustworthy person outside Pharmacia. It was thought that Torvard Laurent was best suited for the assignment. Balazs considered it an excellent idea, and after a moment’s reflection, Laurent agreed.
Pharmacia at the beginning of the 1970’s

Let us, before continuing with the Healon project, take a closer look at Pharmacia at the beginning of the 1970’s. The company, which was founded in 1911, had by this point of time experienced a period of 25 years of uninterrupted growth. This growth was mainly based on the successful launching of Salazopyrin®, an anti-inflammatory drug used in the treatment of inflammatory bowel diseases, and the dextran-based infusion solutions Macrodex® and Rheomacrodex®. These products were examples of close cooperation between Pharmacia and researchers at Uppsala University and KI. Continued collaboration with the research community, particularly research groups at Uppsala University, made it possible for Pharmacia to diversify its operations during the 1960’s and enter into new areas of research, such as separation technology and diagnostics. In 1967, the subsidiary Pharmacia Fine Chemicals was created, based on Sephadex®, a dextran-based product for gel filtration. In 1970 Pharmacia launched its first diagnostics product, Phadebase® Amylase Test, which led to the start-up of Pharmacia Diagnostics in 1975.

Despite successful spin-offs within separation technology and diagnostics, there were serious concerns about the future of Pharmacia at the beginning of the 1970’s. Of key concern was the fact that the company had not managed to develop a new pharmaceutical of any significance during a ten-year period, despite heavy investments in internal R&D. The old products were still quite competitive, but could not be relied upon as a base for future expansion. The management team felt a strong need to find new pharmaceuticals with great market potential. If these new pharmaceuticals could not be created by the company’s own researchers, they had to be acquired from external research environments.

It was under these conditions, and at this time, on August 9, 1971, that Gösta Virding found a letter from Torvard Laurent in his mailbox.
CHAPTER 2: The Healon project is adopted by Pharmacia

A door-opening letter

In the letter, Torvard Laurent introduced his colleague, Endre Balazs, and his research: Balazs had devoted 30 years of work with polysaccharides, and had paid special interest in hyaluronic acid, a macromolecule that can be found in the connective tissues: the cornea, the umbilical cord and the synovial fluid. Balazs had developed a method to produce pyrogen-free hyaluronic acid, and had tried it on different types of joint diseases. Areas where hyaluronic acid was believed to have large potential as a pharmaceutical included eye surgery, orthopedic surgery, rheumatoid arthritis, and traumatic joint conditions among humans and horses, race horses in particular.

Laurent also mentioned that Balazs intended to apply for a patent for the manufacturing method, and that he had started a company, Biotrics, where he would produce large volumes of hyaluronic acid. A trademark for his product had even been applied for.

Laurent mentioned three possible forms of co-operation that Balazs was prepared to consider:

- That Pharmacia functions as a distributor of hyaluronic acid.
- That Pharmacia buys hyaluronic acid in bulk from Balazs
- That Pharmacia produces and sells hyaluronic acid on license from Balazs

After having read Laurent’s letter, Virding acted exactly as Harry Hint had predicted, or at least had hoped.

Without knowing the details, we can imagine the following conversation:

- “Harry, can you come to my office? I have a letter that I would like you to have a look at”,

Hint comes to Virding’s office, reads the letter and says:

- “Very interesting indeed. How do you want me to proceed?”

- “It would be excellent if you developed a project proposal which you then present to the Screening Committee. From there on, we will see.”

Initially everything goes according to plan

Hint quickly produces the suggested project proposal – likely with great help from the extensive documentation received from Balazs – and sends it to the members of the
Screening Committee. The committee functions as a preparatory body to the Project Evaluation Committee (PEC), which is composed by individuals from the research, production and marketing departments.

In the minutes from the Screening Committee’s meeting at the beginning of September, 1971, the following can be read:

- The indicated areas of application are well-known to Pharmacia
- Existing documentation may be sufficient for a registration application
- If the product can be registered as a drug for joint diseases, there is a potential for large volumes
- A thorough evaluation of the market should be done

The Committee concludes:

- It is an interesting offer
- Considering the huge amount of material that has to be analyzed, a six months’ option should be proposed. The results of the analysis should be discussed by PEC
- Global rights should be requested
- Someone, preferably the CSO (i.e. Harry Hint), should visit Balazs’ laboratory to get additional information about the product

The Screening Committee’s evaluation of Hint’s project proposal is quite positive. A possible explanation for this is Hint’s strong position within the committee as well as within the company as a whole. The fact that Hint knows Balazs from his time as a medical student at KI, or that they have recently met, is something that neither Gösta Virding, nor the members of the Screening Committee are aware of. One could say, from Balazs perspective, that he could not have wished for a better person than Hint to have visited him in Boston.

Hint’s visit to Balazs and Biotrics takes place at the end of November, 1971. His report from the visit makes evident that Balazs has been advised by his economic advisers to give licensing rights to more than one licensee. Exclusivity for Pharmacia is, however, possible. It also appears that Balazs is negotiating with companies in Japan and South Africa. Concerning possible markets, clinical trials and financial issues, Hint presents the following information:

The principal market for the product is different types of joint-related diseases. The global market for these types of diseases as well as injuries is estimated to amount to
approx. 10 million injections per year, which, at a price of 10 US$ per injection would result in annual sales of approximately 100 mUS$\textsuperscript{4}.

Clinical experience of the drug is limited. A medical doctor in South Africa has tried the product on 100 patients, and a French doctor on ten. No documentation from these trials is currently available, however. Hint points out that the project cannot be thoroughly evaluated until extensive and reliable documentation exists. He also mentions that the product has been administered on race horses with great success. The results from these trials have been published in a recognized veterinary journal during 1970.

Concerning economic terms, Balazs is interested in discussing not only Healon, but also the possibilities of research cooperation for other products. Balazs asks for 50,000 US$ up front, and an annual minimum royalty of 50,000 US$, or 10 percent on sales when the product has been launched.

Hint concludes that the product is intended for indications of great interest, it fits well into Pharmacia’s current operations both from a research and marketing perspective, and that there is huge market potential. Balazs has extensive expertise in the different fields of research involved, and the offer should be considered an acquisition of a new line of products rather than merely a traditional license agreement. In order to proceed, Hint suggests that Balazs should be invited to Pharmacia for more consequential negotiations.

**Negotiations end in disappointment**

Back in Uppsala, Harry Hint writes to Balazs on December 3, 1971, and asks for documentation of the clinical trials. The letter ends:

"I would like to arrange a meeting with you in Uppsala in the near future, and the appropriate representatives will get back to you within a week or so."

In a letter to Hint on December 23, 1971, Balazs promises to send the requested documentation as soon as it has been received. He also declares that he is ready to go to Uppsala for further negotiations.

At the beginning of January 1972, Balazs is invited to negotiations in Uppsala on February 8-9. On February 2, he receives a telegram from Hint which reads:

\begin{flushright}
\textbf{Balazs to Hint - February 2, 1972:}
\end{flushright}

\begin{flushright}
\textbf{‘I am ready to go next week to Uppsala to negotiate.’}
\end{flushright}

\textsuperscript{4} Pharmacia’s total sales in 1971 amounted to approximately 33 mUS$
"Expect to meet you about 12:00 on Tues. Feb. 8. You will find a message with details and program at the hotel reception Nya Gillet, Uppsala."

From the message, which Balazs receives when he arrives at the hotel in the morning of February 8, he learns that he will have lunch and dinner with Harry Hint, and in-between there will be a meeting with key persons at Pharmacia within research, production and marketing. At that meeting, three external researchers have also been invited, namely Torvard Laurent together with Sven Olerud and Gösta Arturson, professors at the Uppsala University Hospital. The main theme of the meeting is: On Therapeutic Uses of Hyaluronic Acid Preparations. The three points of discussion are: Use in arthritis – veterinary and human; Use in prevention of postoperative adhesion and burns, and; Use in ophthalmiatrics.

As for the following the day, the message reads:

"...we shall meet you for business discussions at 10.00 a.m. and have lunch between 12.00-1.45 p.m. with our CEO. Afterwards, there will be time for additional discussions. Prof. Laurent asked us to keep your evening free."

Everything runs according to plan until the lunch with CEO, Gösta Virding, on February 9. Balazs had already made his conditions for a license agreement very clear, and they are mentioned in Hint’s report from his Boston visit in November 1971. Virding is well aware of these, in his opinion, unacceptable conditions. He knows, for example, that Balazs is asking for a royalty on net sales of 10 per cent, and informs him that royalties exceeding 3 per cent are out of the question. Balazs leaves the lunch very disappointed, and during the subsequent dinner with Laurent and Hint he informs them that, in spite of their valuable support, a future cooperation with Pharmacia seems unlikely.

Virding’s handling of the negotiations with Balazs had upset Hint. He sends a letter to Virding the following day in which he writes that, judging from the outcome of the negotiations, he had:

“...failed in his attempts to present the medical value of the project and Dr. Balazs’ role in the development of the product.”

Hint reminds Virding of lost opportunities in the past and makes the following comments with respect to Balazs’ offer:

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5 Pharmacia, through Virding’s active participation, turned down Xylocaine® in the 1940’s. The product instead became a blockbuster at Astra (today Astra-Zeneca).
- It is a completely new medical discovery. The medical value can be compared to that of cortisone within certain fields of application.
- Is is a product much more developed than is usually the case in connection with license offers. The production technology is fully developed and production is up and running.
- Development costs for possible competitors are estimated to amount to approx. 2 mUS$ and two years of hard work. Additional development costs for Pharmacia would amount to 40-100,000 US$.
- Balazs is not dependent on Pharmacia’s support for biological development since he has access to “... a considerably larger (90 employees), more efficient and better equipped unit than our department for biological research.”

Harry Hint concludes:

“It was a pity to miss such a good opportunity.”

The project survives and evaluations continue

Harry Hint achieves his intended goal with the letter. Virding responds by asking him to make a careful examination of efforts necessary to develop Healon within Pharmacia, to calculate expected return on investment, and thereafter invite Balazs to new negotiations.

Balazs, on his side, does not seem to have become too put off by Virding’s stubborn attitude. On February 29, 1972, he writes a letter that begins: “Dear Harry” - (the first time he addresses his colleague by his first name). Balazs then goes on to express his satisfaction with the meeting in Uppsala, and continues:

”I certainly hope that eventually an agreement will be forged between Pharmacia and Biotrics for the benefit of all.”

A letter dated March 22, 1972 confirms Virding’s interest in continuing the dialogue with Balazs. Virding writes:

”Dear Dr. Balazs: On your visit here we agreed to meet on April 13 in Boston to continue our discussions about a future cooperation between you and Pharmacia.”

The letter also makes clear that Virding will travel to New York via Peking, and that he can visit Boston during the day on April 13:

”I sincerely hope that we will be able to reach a preliminary agreement with you to form a base for a formal agreement.”
At a PEC meeting toward the end of April, Hint presents a report which contains an estimation of the market potential for Healon and the resources needed for organizing a new R&D unit specialized on hyaluronic acid and for conducting necessary clinical trials.

### Healon’s market potential

Previous calculations made by Balazs and his team indicate that the global market for joint disorders likely exceeded 200 mUS$. The U.S. market alone was estimated to total 70mUS$, which is twice as much as Pharmacia’s total sales in 1971. In preparation for the PEC-meeting, Pharmacia’s marketing department had prepared market estimates independent of Balazs’ previous calculations. Frequencies of relevant ailments were calculated on a national and global basis stemming from a study of a specific Swedish region. By adjusting collected data according to the organization of health care and Pharmacia’s competitive strength in different countries, the following estimations were made:

- The global market for knee osteoarthritis amounts to at least 15 mUS$.
- If ten percent of all the patients in the industrialized world suffering from rheumatoid arthritis were treated with Healon three times per year, total sales would amount to 75 mUS$. This is mere speculation as there is no clinical proof that Healon has an effect on such ailments.
- For other potential Healon-treated ailments on the human market, a sales volume of 4.2 mUS$ seems reasonable to expect.
- The veterinary market, in particular race horses, is estimated to amount to between 1.7–5 mUS$.

### Necessary R&D efforts and estimated time until launch

In connection with discussing necessary R&D efforts, Harry Hint reported that the directors of the clinical trials and toxicology departments were very satisfied with the background material provided by Balazs. They expected Healon to become a prominent actor within a field where adequate treatment was currently lacking.

Estimated costs for R&D for toxicology, clinical trials, pharmacology, analysis and control were expected to amount to around 0.2 mUS$. The time needed to produce a registration application was estimated to be two years. A launch for the human market was expected to take place in June 1976, provided that the project could get going within the next few months. Launching for the veterinary market could take place in June 1974.
When interviewed in the autumn of 1977, the director of clinical trials, Holger Derblom, insisted that Hint had misinterpreted him. He did not consider Balazs’ claims to be well-documented as a whole. His earlier proclaimed satisfaction concerned only the pre-clinical documentation. A pre-requisite for a successful launching of Healon was that the claimed effects of the product could be confirmed by full-scale clinical trials – a reservation not mentioned by Hint in his report. Derblom also mentioned that his first contact with Healon was in February 1972, when he was asked by Hint to contact three Swedish medical doctors who had already tried Healon on patients during the 1960’s. Two of them reported negative experiences. The third doctor, who was the one with the most experience of the product, was quite positive. The results of the inquiry had been reported to Hint.

**Option agreement signed**

Preserved correspondences show that there was frequent contact between the parties during this period. In a letter from Balazs to Hint, dated April 28 1972, it appears that Balazs plans to follow up Virding’s visit to Boston in April by visiting Sweden at the beginning of May:

“...to continue negotiations with Pharmacia … Please let me know which day would be most convenient for my visit.”

A couple of meetings take place before an agreement is reached in September 1972. When Endre Balazs and I talked about this initial phase of the cooperation in November 2012, he recalled that a majority of the meetings concerning the license agreement took place in Boston. A likely reason for this was that Virding was very fond of visiting Boston, where he had spent a year at MIT (Massachusetts Institute of Technology) after having finished his studies in chemical engineering at the Royal Institute of Engineering in Stockholm in 1938. Virding always came alone to these meetings, while Balazs was accompanied by representatives of one of Boston’s leading law firms with extensive experience of negotiating license agreements for researchers at MIT and Harvard University.

The original agreement proposal, which was drafted by Balazs and his legal counselor, was sent to Pharmacia on June 23, 1972. Virding returned a revised version on July 5, to which the counselor responded through a letter sent by “air mail, special delivery” on July 14. The accompanying letter indicated that an agreement was close at hand:

"Dr. Balazs and I have carefully considered your comments and suggested revisions, and Biotrics is willing to accept most of your suggestions."

In the minutes from a Pharmacia board meeting on September 12, 1972 it can be read:
“The CEO reported that Dr. Balazs has signed the proposed agreement with Pharmacia.”

The agreement, which is valid from October 1, 1972, is detailed, extensive (40 pages) and based on U.S. law (“…shall be governed by, and interpreted in accordance with, the law of the Commonwealth of Massachusetts, United States of America”). It is a so-called “option to license agreement” (OLA), with a validity of 12 months, between Pharmacia and Biotrics, Inc., a company fully owned by Endre Balazs. Pharmacia would then pay 20,000 US$ under the condition that all existing know-how is delivered within 30 days. Upon expiration of the contract, Pharmacia could choose to extend the OLA for 6 months at an additional fee of 10,000 US$, terminate the co-operation, or enter into a license agreement. The agreement is world-wide with the exception of USA, Canada and South Africa.

If the OLA was turned into a license agreement, there would be a minimum royalty of 20,000 US$ during the first year, later to be increased by 10,000 US$ per year. Minimum royalties would be deducted from royalties on net sales, which are deemed to be 8 percent during the initial five years, 6 percent during the subsequent five years, and then 5 percent. If the license agreement was still intact after 17 years, there would be a royalty of 5 percent on markets where there is a patent, and 0,5 percent on those markets without a patent.

Concerning the “products” of the agreement, i.e. Healon, the following demarcation is made:

“Products’ does not, however, include hyaluronic acid cross-linked to itself or to other substances.”

This is a demarcation that will later prove to be extremely important.

In addition to the payment clauses, Biotrics commits to deliver, and Pharmacia to buy, at least 20 grams of hyaluronic acid at a price of 0.50 US$ per milligram\(^6\), for a total payment of 10,000 US$.

When interviewed in the autumn of 1977, Gösta Virding recalls that he signed the agreement with a feeling of great confidence. He was convinced that there existed a functioning manufacturing method and that the only thing that remained was to conduct a number of clinical trials to confirm the effects of the product. His confidence was mainly based on the information he had received from his Chief Scientific Officer, Harry Hint, and the trust he had in him.

\(^6\) The price per kilogram = 500,000 US$
CHAPTER 3: Promising start followed by unforeseen setbacks

The option to license of October 1, 1972 is celebrated, not least by the “three Musketeers”, Laurent, Balazs and Hint, who can conclude that the project they initiated just over a year before has taken an important step toward realization.

Harry Hint now has to find solutions to the challenges facing the project in terms of production, toxicology, pharmacology and clinical trials. It is also necessary to further analyze the market situation. A first step is to recruit competent individuals to the project. Marianne Granat, a pharmacist employed at Pharmacia since 1968, is appointed project leader. She is assisted by experts from the production department, which allocates three full-time positions, and the R&D department, which allocates ten full-time positions. “Project H” had quickly become the most resource-demanding development project within Pharmacia’s pharmaceutical division during 1973.

On September 15, 1972 Hint writes to Balazs:

”Dear Endre, I heard today from Virding that the contract is signed and sent to you, including the option fee. I will try to do my best to get things going here with minimum delay. The first item we need is the description of the production methods.”

Hint tells Balazs that he will soon send production specialists to Boston. He also mentions the appointment of Marianne Granat as project leader. Balazs responds within a couple of weeks, and informs Hint that he plans to visit Uppsala on October 19 to deliver the requested documentation concerning the production method and:

”…to meet Mrs. Granat and start planning production, as well as preparing for the November visit of the Pharmacia staff.”

Marianne Granat then visits Biotrics in Boston during five weeks in November-December 1972 and collects available chemical, pharmacological, toxicological and clinical documentation about Healon. While she is at Biotrics, Pharmacia’s production director also visits the company together with one of his associates. Granat reports that there is a large body of scientific knowledge at Biotrics. She also reports that Biotrics has provided Pharmacia with a detailed production manual, which has been studied on site by representatives of Pharmacia’s production department. Lastly, she points out that the clinical trials will be conducted with hyaluronic acid produced by Biotrics. The tone of her report is very positive.
Status report, February 1973

At the beginning of February, 1973, Marianne Granat delivers her first status report on the Healon project to Pharmacia’s board of directors. She reports that extensive documentation received from Balazs is still under evaluation, meaning that planned activities concerning pharmacology, toxicology, immunology and pharmacy have not yet begun. The objective is to carry out sufficient analysis in order to be able to make a decision in September 1973, when the OLA is set to be renegotiated.

During the same meeting, the production director reports that a thorough assessment of Balazs’ production methods has revealed that direct application of the methods is technically feasible, but cannot be recommended due to various technical deficiencies. A new production unit is being designed, and should be operational by the end of 1974.

The following quotation from a letter on April 3, 1973, shows that Balazs is actively involved in the knowledge transferring process. It also indicates that he has recently visited Uppsala:

"Dear Harry, It was good to see you in Uppsala and I was quite impressed by the progress made on hyaluronic acid at Pharmacia and with the number of people involved in the project. If we continue with this speed and efficiency, I have no doubt that we will get good results…. With warmest personal regards, As ever, Endre."

Clouds begin to gather on the horizon

The difficulties related to Balazs’ production methods are brought up again by the production director (PD) at a meeting with the Project Evaluation Committee in May 1973. From the minutes of this meeting:

"PD underlined the present difficulties in adapting Dr. Balazs’ rather empirical and incompletely specified production methods to industrial conditions. A considerable amount of work remains to be done on the production process, much more than anticipated when the option agreement was signed. We therefore have good reasons for a prolongation of the option period with 6 months, thus postponing the final license agreement."

The committee’s recommendation is followed, and at a meeting between Gösta Virding and Endre Balazs in August 1973, it is agreed that the OLA shall be extended by 6 months, to March 31, 1974. According to the initial agreement, Pharmacia paid Biotrics an additional fee of 10,000 US$.

At the end of September, 1973, Marianne Granat presented her second status report to Pharmacia’s board of directors, under the following headings:
Clinical trials

Clinical trials are being carried out on 120 patients at three different Swedish hospitals. All the trials concentrate on knees, as the knee is the most vulnerable joint. Previous studies made by Balazs also indicate that the area of knees is where Healon can be expected to have its best effect. Only pre-clinical results are available, and it is therefore too early to draw any conclusions. Final results are expected to be available in February 1974. Additional clinical trials are being planned.

Production

Documentation on production methods lacks important information concerning performance at different steps of the production process. The fact that the information is contradictory at times further complicates the technical evaluation. In spite of these difficulties the situation is deemed to be under control. Pre-planning is expected to be ready by the end of January 1974, and full-scale production should be possible at the end of 1975. This is 12 months later than what was estimated in February 1973, seven months earlier.

Market

The marketing department is to present a sales forecast, which assumes launching on the human market during the first quarter of 1976. Total sales during 1980 are estimated to be between 8-11 mUS$. This forecast does not include the US, Canada and South Africa as these markets are not included in the OLA.

From the board meeting minutes:

“The results of the ongoing clinical trials are decisive for the project’s further fate. Not until these results are known can the market potential for Healon and necessary further development efforts be calculated with greater certainty. The extended OLA will expire on March 31, 1974, and before this date it must be decided whether or not Pharmacia should sign the final license agreement.”

In November 1973, the project evaluation committee concludes that the Healon project is under substantial time pressure, primarily because of the design of the agreement. There is a high degree of uncertainty both with respect to the production methods and the clinical effects of the product. Results from the ongoing clinical trials are expected to be ready by February 1974. Preliminary results indicate that ambiguous conclusions can be expected. Harry Hint argues that Pharmacia seems to be involved in clinical research on Healon rather than clinical trials. In particular, much of the uncertainty
concerns the dosage of the product, how the selection of patients should be made, and how the effects of treatment should be evaluated. Thus far in the ongoing clinical trials a very high placebo effect has been reported. Suggested design of clinical trials received from Balazs and recommended dosage size have not been possible to apply.
CHAPTER 4: License agreement with restrictions

In February 1974, Marianne Granat presents her third status report to the project evaluation committee. It includes, among other things, a new time frame for the project and a new sales forecast. Production start has been postponed by another six months as compared to the status report of September 1973, and launching on the human market has been moved from the first to the fourth quarter of 1976. As for clinical trials, it is made clear that preliminary results from trials on horses indicate positive effects, while the preliminary results from ongoing human trials are more difficult to interpret. The new sales forecast is less optimistic than the previous one. Estimated sales in 1980 have been reduced from 8-11 mUS$ to 6.4-7.2 mUS$. The horse market is estimated at approximately 0.8 mUS$.

With reference to the information given in the status report, the Project Evaluation Committee recommends an extension of the OLA for another six months. If this cannot be achieved, the license agreement should be signed.

The board of directors, which met on March 12, 1974, concludes that reported results from trials on horses can be interpreted as positive, “beyond any reasonable doubt”. The horse trials have been conducted by the chief veterinarian at the leading racetrack in Sweden, Solvalla, and another Swedish equine veterinarian, who is also director of toxicology at Pharmacia. Regarding human trials, final results are expected to be received by September 1974. The minutes of the meeting read:

“It has proven to be much more difficult than was originally thought to show significant effect of Healon on humans according to the established protocol. However, the medical doctors involved in the trials, internal as well as external, are still very positive to the drug.”

At the board meeting, CEO Gösta Virding emphasizes the importance of avoiding further limitations on the geographical scope of the agreement, in particular Japan. It is also important to come to an agreement concerning the U.S. He considers therefore further extension of the OLA as far too risky. Possible cost savings do not balance the commercial risks involved. The board agrees with the CEO’s reservations and concludes that Pharmacia should try to attain a license agreement at the expiration of the OLA on March 31, 1974.

This decision is never implemented. For different reasons Endre Balazs is unable to visit Pharmacia for planned negotiations at the end of April, 1974. Meanwhile, a new evaluation is made on the production conditions. The subsequent results cause Gösta Virding to reevaluate his stance, and he suggests a second extension of the OLA until
30 September, 1974. The agreement is accepted by Balazs, who receives 10,000 US$ as payment for the extension plus another 10,000 US$ as advanced payment of future royalties. By this point, Pharmacia has paid Biotrics 50,000 US$, excluding payment for hyaluronic acid delivered for clinical trials.

In March 1974, Pharmacia is reorganized. Gösta Virding becomes president of Pharmacia Group (for a while called Fortia). Also, the three divisions; Pharmaceuticals, Diagnostics and Fine Chemicals are organized as separate subsidiaries. Pharmacia Pharmaceuticals, to which Healon belongs, gets a new, externally recruited CEO, Birger Lövgren. The principal decision-making body of Pharmacia Pharmaceuticals is the “L-group”, which consists of Lövgren, Chief Scientific Officer Harry Hint, and the directors of production, marketing and chemical research. The official start date for the new organization is January 1, 1975, but in practice it starts to operate already in March 1974.

Status of clinical trials and reflections ahead of license negotiations

A couple of weeks prior to the October 1974 negotiations for a final license agreement, the department of clinical trials presents a status report of completed and ongoing clinical trials. The report shows that the therapeutic value of the product is quite differently assessed by the clinics involved. Five of the trials have been completed, and five are still ongoing. Different dosages have been used, and there is uncertainty about the optimal dosage level. The department is unable to assess the therapeutic value of Healon for disorders in the knee joint until all trials have been completed.

Ahead of the license agreement negotiations with Balazs, the project leader Marianne Granat presents a document entitled, “Thoughts in view of the final negotiations with Professor B”. The document is shared with Gösta Virding, the new CEO of Pharmacia Pharmaceuticals, Birger Lövgren, Harry Hint and the director of chemical research, Tore Natvig. According to Granat’s opinion, the “product” originally acquired from Balazs should be considered merely a product idea. When the first OLA was signed in 1972, the general belief at Pharmacia was that the company had acquired a complete product with production methods, control criteria and sufficient documentation concerning pharmacology and toxicology to make possible world-wide registration of Healon. What was thought to have remained for Pharmacia was verifying clinical trials according to an established protocol. The reality, Granat argues, has turned out to be quite different.

Further, Marianne Granat claims that Biotrics has not been able to produce and deliver sufficient quantities of Healon since the production process has not been under control. As a result, a delay of 1-1.5 years has been seen. The original idea was to register,
produce and sell a more or less existing product, and Pharmacia thought they could rely on Dr. Balazs’ know-how without too much internal research. Given the unforeseen difficulties, focus has now shifted to register, produce and market a product primarily developed at Pharmacia.

The report concludes:

- Virtually all development work has been done by Pharmacia
- Additional protection for the product aside from internal knowledge does not exist
- Pharmacia has paid quite a lot for generally available knowledge
- The experience and knowledge added by Pharmacia should be of such a big value to Biotrics that a geographical extension of the agreement should be possible without any additional payment

Marianne Granat’s thoughts above can be compared with the impressions she reported from her first visit to Biotrics a little less than two years earlier (see Chapter 3). She then talked about the large body of scientific knowledge at Biotrics, and that Pharmacia had received a detailed production manual.

**Details of license agreement**

At the license agreement negotiations, which took place on October 30, 1974, Pharmacia is represented by Gösta Virding, as Birger Lövgren is not yet sufficiently familiar with the project. When interviewed in 1977, Virding revealed that he was seriously considering terminating the collaboration with Endre Balazs based on the information he had received on the project’s progress and results. After talking to Harry Hint, who was steadfast in his belief in Healon and Balazs, Virding decided to go ahead and sign the agreement.

The license agreement implies that Pharmacia is to gain world-wide rights to produce and sell Healon with the exception of the U.S., Canada and South Africa. The economic conditions of the agreement, to last 17 years, are basically the same as those established in the original OLA. This means that Biotrics is to receive a down-payment of 20,000 US$ and a minimum royalty of 20,000 US$, to be increased by 10,000 US$ per year. A revenue-based royalty is also agreed upon, starting at 8 percent during an initial five-year period, decreasing to 6 percent during the next five-year period, and finishing at 5 percent until the termination of the agreement.
With the license agreement Pharmacia has paid Biotrics/Balazs a total of 80,000 US$. Pharmacia’s total investments in the Healon project by the end of 1974 amount to approximately 1.5 mUS$. 
CHAPTER 5: License agreement re-negotiated

The signing of the license agreement requires immediate acceleration of all activity related to Healon. A full-scale production plant has to be built and remaining clinical trials have to be completed. Not until registration for the human indication has been granted can Healon be launched. In January 1975, the following timetable is established for the project:

- March/April -75 Planning of a full-scale production plant starts
- May -75: Evaluation of clinical trials completed
- July -75: Initial work on production plant starts (to be built in the existing production building)
- August -75: Swedish registration application submitted
- October -75: Final decision concerning the production plant
- September -76: Production of first batches in full-scale production plant
- First quarter -77: Launching on the human market

In February 1975, the L-group decides to allocate 170,000 US$ for initial planning and construction work.

When Pharmacia’s new organization formally enters into force on January 1, 1975, Birger Lövgren, the new CEO of Pharmacia Pharmaceuticals, replaces Gösta Virding as Pharmacia’s chief negotiator. In his role as CEO of the entire group, Virding continues, however, to participate in the talks with Balazs.

Lövgren is dissatisfied that the license agreement does not include the U.S., Canada and South Africa, and initiates dialogue with Balazs about this. Correspondence between Lövgren and Balazs during the spring of 1975 shows that the idea of a separate license agreement is entertained. The agreement would pertain to North and South America and would involve Pharmacia’s subsidiary in the U.S., Pharmacia Laboratories, in combination with starting a jointly owned R&D company, Biotrics, USA. The idea is further discussed when Virding visits Boston in May, but as per a letter dated July 8, 1975, Balazs learns that for tax and legal reasons Pharmacia prefers a different solution. Endre Balazs is then invited for further discussions with Birger Lövgren and his associates in Uppsala, before returning to Boston from a longer visit to Europe at the end of the summer.

In a July 2, 1975 letter to Endre Balazs, Harry Hint expresses complaints about the documentation delivered by Biotrics in connection with the Swedish registration application. Hint requests documentation from half a dozen investigations, and concludes:
“We do realize the amount of work that we request from you, but we feel that it is necessary to round off the application.”

Dialogue and meetings between Birger Lövgren and Endre Balazs continue during the autumn of 1975. Until the summer of 1975, the letters to Balazs are addressed to Boston Biomedical Research Institute, but from August 1975 Balazs has a new address: Department of Ophthalmology, College of Physicians and Surgeons, Columbia University, New York. Balazs has been appointed “Director of Eye Research” and Malcolm P. Aldrich Professor in Ophthalmology.

**Ambiguous results from clinical trials**

At this point, CEO Birger Lövgren was anxious to obtain a license agreement that included North America. However, before entering into further negotiations, he must first be sure that the product meets all registration criteria set by the Swedish National Board of Health and Welfare. To this end, he orders that work relating to the registration application shall be given the highest priority. At a meeting of the project evaluation committee in August 1975, Marianne Granat reports that the submission of the application must be postponed from September to December 1975 due to delays in the clinical trials. A month later, further postponement is decided. The latest delay sees an application submission no earlier than March 1976, due to, among other things, difficulties in interpreting the results of completed clinical trials and the high placebo effects reported in many of the trials.

In September 1975, the doctors responsible for ten completed or ongoing clinical trials are invited to a meeting at Pharmacia. Attitudes toward the drug vary widely, from very positive to negative. Eight clinical trials have been completed. In four of these, the drug has been injected only once. Significant positive effects have not been experienced at all when compared to the control groups. Of the remaining four clinical trials, all of which performed with repeated injections and different dosages, two have achieved significant positive effects, one a non-significant positive effect, and one no effect, in comparison with the control groups. Two clinical trials are still ongoing.

In October 1975, the L-group of Pharmacia Pharmaceuticals decides to postpone any decisions on investments for the production plant until the results of the two remaining clinical trials have been reported, meaning a further delay of 7-8 months. The project leader, Marianne Granat, strongly disagrees, as this will drastically affect the agreed-upon timetable. She discusses the matter with Birger Lövgren and Harry Hint, and in November 1975 the members of the L-group decide to revise their decision from a month earlier. It was possible to make a preliminary evaluation of the two ongoing clinical trials in January 1976. Based on this evaluation, the investment decision could
be made. When interviewed in December 1977, the director of clinical trials claimed that there was no reason to believe that the remaining trials would have any influence on the possibility of the product becoming registered.

In December 1975, it is decided that negotiations concerning a revised license agreement will take place in Uppsala in January 1976. This decision is preceded by several meetings, and a frequent correspondence between Birger Lövgren and Endre Balazs during the late autumn of 1975. Endre Balazs relationship with Birger Lövgren becomes more personal than that with Gösta Virding and Harry Hint. As far as Balazs can recall, he was never invited home to any of the latter two. Balazs and his future wife Janet were invited to Lövgren’s home early on. In October 1975 Balazs writes to Lövgren:

"Dear Birger, Janet and I enjoyed tremendously our visit at your home. I am very grateful to you and Margareta for your kind hospitality."

In the letter, Balazs goes on to suggest suitable dates for further discussions in New York in November, and concludes:

"I am in the process of preparing a summary of our discussion as I remember it, and further suggestions to reach an agreement. I will send this to you next week."

The discussions between Balazs and Lövgren in November went well, judging from a letter between the two from November 21, 1975. The letter deals primarily with the experiences from the first clinical trial in the U.S. on patients with knee joint disorders, and Balazs mentions possible explanations as to why the placebo effect varies to such a great extent between different patient groups. Balazs concludes:

"We are presently working on the budget of the first year of our cooperative work in the Western Hemisphere. Our aim is to have it reach your desk before the end of the month."

On January 29, 1976, a new, extended license agreement is signed between Pharmacia AB and Biotrics, Inc. The new agreement, due to take effect on January 1, 1976, contains several main amendments:

- The agreement includes the US and Canada, making it virtually worldwide. The only missing geographical area is South Africa and some of its neighboring countries
- The agreement has a duration of ten years, "from the start of commercial sales" in countries in which there is no patent. In countries with a patent the agreement is valid until the expiration of the patent
The minimum royalty is raised to 100,000 US$, runs until 1985, and is index-linked from 1979.

The royalty on sales is lowered to 4.2 per cent, further reduced to 1 per cent after ten years in countries where a patent is present, and until the expiration of the patent.
CHAPTER 6: New production plant - an ill-conceived decision

The decision to build a new production unit for Healon, scheduled for October 1975, has been postponed. Before construction can begin, updated information about clinical trials, the market situation and the profitability of the project must be presented. The investment is of such magnitude that the Group Board of Directors must confirm the L-group’s decision on the matter.

Remaining concerns with clinical trials

In January 1976, results from the two remaining clinical trials are presented. In neither of these has any significant, positive effect been found. This forces Pharmacia’s Director of Control, responsible for contact with the Swedish National Board of Health and Welfare, to concede that the results from the clinical trials are not sufficient for a registration of the product for human use. She therefore recommends a separate application for veterinary use. The clinical data for an application for veterinary use originate from a study of 46 Swedish racehorses treated with Healon. However, one disadvantage of the study is that it was not a controlled study. Another disadvantage, according to the Director of Control, is that this is the only study that can be referred to in the application. She concludes:

“Whether or not there is sufficient data for an application must be assessed by the CSO and the Director of Toxicology. If they do not find it too risky, I would strongly recommend the submission of a separate application for veterinary use during this spring.”

The Director of the Department of Clinical Trials, Holger Derblom, has already expressed concerns over the fact that only a single clinical trial on horses has been made, and that it was not a controlled trial. In response, the Director of Toxicology, Gert Lindblad, maintains that because of practical reasons it is not feasible to conduct controlled trials on horses. The methodology that has been used has furthermore been approved by an expert at the National Board of Health and Welfare who is expected to be involved in the assessment of the application. What further concerns Derblom is that one of the two veterinarians behind the only existing clinical trial is the previously mentioned Director of Toxicology, Gert Lindblad. How will this influence the decision of the National Board of Health and Welfare?

During a meeting on February 16, 1976 the L-group follows the recommendation of the Director of Control, which has also been approved by Harry Hint and Gert
Lindblad, and decides that a separate application concerning Healon for veterinary use shall be submitted no later than April 15, 1976. Before an application for human use can be submitted, the L-group finds it necessary to clarify the properties of the product and its curative effects. To receive such clarifications, the L-group decides to refer the project to the Department for Explorative Medicine. This is a department that has had very little involvement thus far in the Healon project.

Despite large uncertainty regarding when Healon can be approved for use in humans, the L-group is prepared to discuss the future of the production plant at their next meeting, on March 1, 1976. As a basis for a decision, project leader Marianne Granat is asked to provide an updated sales forecast for the veterinary market, the only market that can be expected to generate any income in the near future, and a calculation of the profitability of the project.

**Forecasting sales on the veterinary market**

At the project leader’s request, the Marketing Department produces a sales forecast for the veterinary market. The L-group’s somewhat confusing instructions stem from the decision to build a new production plant for Healon being based on expected sales from the veterinary market. Even so, no investments would be made unless the product was also expected to be launched on the human market within the foreseeable future.

I was personally involved in the preparation of the forecast, which was based on statistical data on the number of race-horses in different countries, reported frequencies of different types of leg injuries, and claimed therapeutic effects of Healon. The time it took to have an application approved varied considerably between different countries. In France, the product was already approved for use on horses, and the product could be launched as soon as it was deemed appropriate. In Sweden, the registration time for veterinary use was as long as for human use.

The realistic forecast (there was also an optimistic and a pessimistic forecast) indicated sales on a global scale amounting to 0.3, 1.2 and 3.6 mUS$ for the years 1977, 1980 and 1986. This was considerably lower than the marketing department’s estimation of the size of the veterinary market in April 1972, which was 1.7–5 mUS$.
**Profitability**

Based on the sales forecast, the profitability of the project was also calculated. The cost of building the production plant was estimated to be 2.1 mUS$, 0.44 million of which was reserved for unforeseen costs. What had already been invested in the project, approximately 2.3 mUS$, was viewed as a so-called sunk cost. The first delivery was expected to take place in November 1977.

For the period 1977-86 the project was expected to generate a profit of 9 mUS$, and payoff was estimated at between 6 and 10 years.

A calculation based on the assumption that it would be possible to launch Healon on the human market within a couple of years indicated a possible profit of 40 mUS$ for the period 1977-86.

**Production plant receives the green light and the project leader quits**

At a March 1, 1976 meeting, the L-group decides to ask for the Group Board of Director’s approval regarding an investment of 2.1 mUS$ for the construction of a production plant for Healon. In the minutes from the board meeting of March 16, 1976, the following can be extracted:

“CEO emphasized that although the veterinary market could be profitable in itself, this decision would not have been made had it been established that the drug has no effect on humans. However, since there are good reasons to expect that proof of effect will also be found on humans, we should make use of the benefits offered by the veterinary indication, namely, in addition to its own profitability, the saving of time it offers at the prospect of a future launch of the product on the human market. This is important, particularly when considering that the product cannot be expected to be protected by a patent… The Board decided that the suggested investment should be made.”

After having participated in the Group board meeting on March 16, 1976, Marianne Granat leaves her assignment as project leader for the Healon project and ends her employment at Pharmacia.
Continued slow development of the Healon project, 1976-77

Construction of the production plant began immediately after the investment decision had been made. In April 1976, the application for veterinary use was submitted to the Swedish National Board of Health and Welfare. Later that spring, the Marketing Department, together with Pharmacia’s subsidiary in France, decided to launch Healon on the French racehorse market in conjunction with the annual congress of the French veterinarians in October 1976. The expected demand for syringes was to be met by the production under way at the pilot plant. The sales target for the French racehorse market for 1977 was 0.3 mUS$.

In February 1977 the Swedish National Board of Health and Welfare reported that the clinical results presented in the application for veterinary use were insufficient. Further clinical documentation had to be presented before approval could be given.

In November of 1977, Healon was launched on the Australian racehorse market, later than originally planned. Total sales on the French and Australian racehorse markets during 1977 amounted to 0.05 mUS$, bleak results when compared to budgeted 0.3 mUS$.

Concerning the possibility of getting an approval for the human market, additional research was needed before an application could be produced. A clinical trial had begun in the U.S. and was expected to be ready by September 1978. The outcome of this trial was expected to determine the future of the Healon project.

Project status, late 1977

By late autumn of 1977, the Healon project had very few supporters. Perhaps this should have come to no surprise, considering the development of the project compared with expectations when the first option to license was signed in September 1972. The focus then was on the human market, a launch was expected to take place in June 1976, and the market for knee joint osteoarthritis alone was estimated at 70 mSEK. Pharmacia had nearly completed construction of a costly new production plant that stood still as no application for Healon use on humans was able to be prepared due to conflicting results from a large number of clinical trials. Launching of the product on the human market could not be expected to take place until well into the 1980’s. In addition, the Swedish application for registration of the product for veterinary use had been rejected. The only income that had been generated was tiny 0.2 mSEK from the French racehorse market.

Among those who advocated an immediate liquidation of Healon was one of the members of the L-group, a medical doctor who had recently joined Pharmacia, and
who was the inventor of a wound-care product that the company had launched on the market in 1977. The project’s biggest supporter and protector was still Harry Hint, but also he realized that the end was near unless something unexpected and drastic happened. And something unexpected would in fact happen. But before we turn to this new and exciting chapter of the Healon saga, let me say a few words about my own involvement and interest in the Healon project.
CHAPTER 7: My own participation in the Healon project

During my studies at Uppsala University I worked a couple of days per week at the foreign department of a local bank. Among my duties was to prepare foreign currencies for employees in the International Department of Pharmacia. My clients were friendly, well-dressed and professional people in their early thirties, and from the composition of their foreign currencies, I understood that they could visit four to five countries on different continents during a single trip – what an exciting life! I became curious, read about the company and realized that it was a place where I would like to work. A couple of years later my dream came true. I was employed at Pharmacia in the spring of 1973, and at the beginning of 1975, at which time I was head of the Marketing Service Department, I accepted an offer to become product manager of Healon. Pharmacia had acquired the hyaluronic acid-based product on license a few years earlier. My rudimentary knowledge of hyaluronic acid and licensing was about to be put to the test.

Experiences as the first product manager of Healon

Healon belonged to the same product group as dextrains, which included Macrodex and Rheomacrodex, two flagships in the product portfolio of the Pharmaceutical division. The head of the product group was Erik Danielsson, who nine years later became the CEO of the entire company. I started my job as product manager shortly after Pharmacia had signed the first license agreement with Biotrics - the one that did not include North America. To start with, the sole focus of the project was on knee joints. In other words, our task was to develop a marketing strategy for a pharmaceutical that was believed to revolutionize the treatment of osteoarthritis in the knee joint and other joints of the human body. In order to develop a successful strategy, it was necessary to learn essentially everything about the product itself and its properties, current treatments of different joint-related diseases and disorders in different parts of the world, and potential competitors.

As time went on, my internal network within the company expanded, and I started to learn about other aspects of the product than only those related to marketing. Relatively soon my colleagues and I in the Marketing Department realized that there was an overhanging risk that the launching of the product on the human market would be delayed, and that we should meanwhile direct our focus toward the racehorse market. The most appropriate market at the time was, suitably enough, France, a country that had more racehorses than any other European country. From the autumn of 1975 and
onwards, most of my work was oriented toward preparing for the launch of Healon on the French veterinary market during the second half of 1976. Much of this work was done in close co-operation with Birger Bergman from the Pharmacia Board of Directors.

A fascinating assignment under increasing frustration

Preparing for the launch of Healon on the French racehorse market was a fascinating assignment. I began more or less as a novice, but quickly learned quite a lot about horses, and particularly about racehorses and horse racing. I understood the economic importance for owners and trainers of valuable horses to have access to a drug that could quickly get a horse back into training and competition. The launching of Healon in France, under the trademark Healonid Vet., was carried out in close cooperation with Pharmacia’s French subsidiary and, as mentioned in the first chapter, French star veterinarian Jean Plainfossé.

The uncertainties that surrounded the Healon project made it difficult to promote the product to the marketing people at the subsidiaries. This was due both to the limited size of the veterinary market – when I spoke of a global market potential in the order of 3-4 mUS$, my colleagues talked about markets ten or twenty times that size – and their limited interest in and knowledge about racehorses. When I spoke to them about Healon’s potential on the human market, a common response was: “Welcome back when the product has been approved.”

In February 1976, Erik Danielsson and I were involved in elaborating sales forecasts and profitability calculations that formed the basis for the investment decision on the production plant. We certainly found it problematic that a decision regarding investment in a production plant would be made before the application for registration had been submitted. We were also concerned about the strong focus on the veterinary market. Our concerns were communicated to top management, and we were pleased to read the CEO’s motivation around the investment decision in the minutes from the board meeting, namely:

“…although the veterinary market could be profitable in itself, this decision would not have been made had it been established that the drug has no effect on humans.”

After having participated in the successful launching of Healonid Vet. on the French veterinary market in October 1976, I decided to take one year off from Pharmacia and return to my academic studies. As a result, I left my position as project manager of Healon at the end of December, 1976.
CHAPTER 8: The Healon project evaluated

During my year off from Pharmacia I studied business management at the postgraduate level at Uppsala University. At the very beginning of that year I read an article written by the Canadian professor and management guru Henry Mintzberg. The title of the article was “The structure of unstructured decision processes”. I discussed the article with my academic supervisor and mentioned that I had practical experience of an unstructured decision process. We both agreed that an evaluation of the Healon project would be an excellent subject for a Master’s thesis. I therefore contacted the CEO of Pharmacia Pharmaceuticals, Birger Lövgren, to get his approval, including full access to the existing documentation on the project. After some consideration from Lövgren’s side, and after he had discussed the matter with the Group CEO, Gösta Virding, I was granted access to the necessary information for the purposes of my thesis. There was a strong interest on Pharmacia’s side to learn from an experience which was thought of as a potential failure.

I carried out the main part of my evaluation of the Healon project during the autumn of 1977, and had unrestricted access to all written documentation about the project. The documents were meticulously organized and catalogued by the project leader, Marianne Granat, until she left the project in March 1976. In addition to written documentation, I collected information by interviewing six key persons involved in the project. They included, Group CEO, Gösta Virding, CEO of Pharmacia AB, Birger Lövgren, CSO Harry Hint, the Director of Chemical Research, Tore Natvig, the Director of Clinical Research, Holger Derblom, and the Project Leader, Marianne Granat.

Analysis of the Healon project, end 1977

In my Master’s thesis, which was presented in December 1977, I analyzed the decision process based on a model containing five different so-called decision hypotheses. The meaning of these hypotheses can be summarized as follows:

The commitment hypothesis

This hypothesis is based on the logic that: you cannot say A without saying B. If you have initiated a project, and especially if you have convinced other people to invest time and money in it, you are the last one to give it up.

7 Mintzberg et al.(1976)
The sponsor hypothesis

A project sponsor, especially a person whom the decision makers trust, can drive a project very far in an organization. It is more often the sponsor him- or herself than the project as such that is being evaluated.

The advantage hypothesis

Most people involved in a project experience some type of personal advantage of their involvement. The advantage can take the form of more challenging tasks, travels, status and/or possibilities of promotion and higher salary. These advantages make an objective evaluation of the project more difficult.

The attitudinal hypothesis

Most organizations prefer optimists to pessimists. A skeptical or critical person is viewed with suspicion. The sponsor is often deeply involved in his or her project, and to question the project is synonymous with questioning the sponsor personally. To express critical thoughts in an environment like this is very difficult.

The filter hypothesis

People at the top management level, CEO’s and similar positions, should only be informed at a general level and not be burdened with details. Referring to the advantage and attitudinal hypotheses, there is an evident risk that the top management will base their judgments and decisions on filtered and biased information.

The Healon project – success or failure?

Was the Healon project a failure? This was a question I asked all the six key persons in December 1977.

The main sponsor of the project, Harry Hint, said that most projects in the pharmaceutical industry are failures in the sense that they never reach the market. He referred to a study of the biggest pharmaceutical companies in the U.S. which showed that of all projects for which clinical trials were run, only 10 percent reached the market. He did not consider the Healon project a failure, since it was still possible that it would be approved as a therapy for both osteoarthritis and other ailments. A remaining challenge was to prove the effect of the drug compared to placebo.

Nor did the Director of Chemical Research, Tore Natvig, look upon the Healon project as a failure. He considered the development of the project relatively normal. To believe that Endre Balazs would provide Pharmacia with a fully developed production method, as some of his colleagues obviously had, was a bit naïve according to Natvig. One had...
to realize that Balazs was a researcher, not a technician. It was true that Harry Hint claimed early on that there existed a well-functioning production method, but Hint, like Balazs, was an expert on research and not on production. From the very beginning, Natvig had been aware that Pharmacia had acquired a mere product idea from Balazs, for which considerable development work remained to be done.

The project leader, Marianne Granat, who left her assignment as well her employment with Pharmacia in March 1976, was of the opinion that Pharmacia had underestimated the development resources needed for the project, and that the company lacked necessary competence within certain areas, such as, for example, clinical trials and market research.

The Group CEO, Gösta Virding, was dissatisfied with the development of the project so far, and thought that the outcome of a recently started clinical trial in the U.S. was of large importance for the further development of the project. This view was shared by Pharmacia AB CEO, Birger Lövgren.

The Director of Clinical Trials, Holger Derblom, held a different opinion. According to him, the results from the ongoing clinical trial in the U.S. would not make much difference. In his view, a major weakness of the project was that decision makers had not received correct information about the clinical trials. Positive results had been overemphasized, and negative results withheld. There had been too much focus on the statistical results of the trials, and insufficient interest in the clinical effects of the drug. This could have been avoided had the Department of Clinical Research been more involved in the presentation of the results.

**Perceptions according to the five hypotheses**

Regarding the commitment hypothesis, Harry Hint was aware of the risk of that he, as main sponsor of the project, would act in a biased way. He had therefore recently decided to play a less prominent role in the project, simply letting facts speak for themselves.

The Director of Clinical Trials, Holger Derblom, had at times felt that he was not committed enough to the project. On one occasion he even asked to be excused from the project altogether in 1975. He was not comfortable playing the role of the Devil’s Advocate, all the while being constantly perceived as a pessimist.

The sponsor hypothesis was generally confirmed. Harry Hint knew that he was looked upon as the main sponsor of the project, which is a risky role to play. On the other hand, you cannot develop a project without a sponsor. And as a sponsor, it is necessary at times to magnify the potential of a given project, especially early on. The decision
makers must be excited and enthusiastic about your project, something not always easily achieved by a simple presentation of dry facts. Hint realized that his opinions and arguments had sometimes been given greater weight than intended. He was therefore glad that the project now had more than one sponsor. The veterinary application, for example, was primarily promoted by the Director of Toxicology, Gert Lindblad.

The advantage and attitudinal hypotheses were reinforcing each other, according to the CSO and the Directors of Chemical and Clinical research, i.e. Hint, Natvig and Derblom. They shared the opinion that the company culture rewarded optimistic and offensive, at times almost aggressive behavior. According to the two CEO’s, Virding and Lövgren, this was a regrettable misperception. Virding admitted that he preferred co-workers with a positive attitude toward the company and its objectives, but he considered it the duty of all not to withhold negative, relevant criticism.

The manner in which results from the clinical trials had been presented seemed to confirm the relevance of the filter hypothesis. Another example was how information had been presented about the veterinary application. If the decision makers had been aware of the doubts that existed at the Department of Clinical Research, additional clinical trials on horses could have been started well in advance. Instead, the news in February 1977 that the application had been rejected came as an unpleasant surprise, and delayed the launch on the Swedish veterinary market by at least one year.

In Birger Lövgren’s opinion, it is impossible for a CEO to absorb all information about a given project. The responsibility of selecting and structuring the information to be presented to top management rests upon one’s co-workers. With skilled co-workers comes an increased likelihood of making good decisions.

**Final reflections**

Something to keep in mind when studying the opinions and thoughts of the six key persons involved in the Healon project at the end of 1977 is the pressure they were under at the time. Total failure was a real possibility and was essentially right around the corner. It was high time to begin looking for scapegoats as opposed to heroes. I am therefore now, more than 37 years later, impressed by the clarity and sincerity that characterize many of the comments made by the key persons. Likely, a contributing factor was the fact that they were all professionals with sufficient confidence and experience. They had participated in similar projects before, and knew that this could very well be yet another in a long line of abandoned projects. Such knowledge is often a prerequisite for the possibility of one day finding a successful project.
My own assessment of the Healon project in December 1977 is revealed by the final sentence in my Master’s thesis report, which is a quotation from a famous Swedish fairy tale about a tailor, who instead of making the coat originally agreed upon, makes a pair of mittens. This quotation would later ring in my head as the project eventually took flight in earnest. Five years after I had completed my evaluation, Healon had captured the position as Pharmacia’s largest product.

What was it that so drastically changed the course of the Healon project? I will return to this question in Part II.

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8 In Swedish: “Det bidde ingen rock, det bidde ett par vantar i stället”
Part II: Healon - a revolution in cataract surgery

CHAPTER 9: The discovery of the cataract surgery market

Toward the end of 1978, decision makers at Pharmacia began to realize that business opportunities for Healon within ophthalmology were larger than previously believed. Healon’s potential in different types of eye surgery was something Endre Balazs had claimed from the very beginning. “Use in ophthalmiatrics” was, as mentioned in Chapter 2, one of three possible therapeutic uses he indicated at the very first meeting between himself and Pharmacia’s researchers in February 1972. The document *Hyaluronic Acid and Matrix Implantation*, which Balazs presented to Pharmacia during the autumn of 1972, contained chapter headings such as “Hyaluronic Acid and Replacement of the Vitreous and Aqueous Humor”, and ”Intravitreal Injection of High

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Molecular Weight Hyaluronic Acid in Retinal Detachment Surgery”. Consequently, the possible use of Healon in connection with eye surgery was not unknown to Pharmacia, as has sometimes been indicated. What is correct, however, is that eye surgery was not considered particularly interesting from a business point of view, neither by Balazs, nor Pharmacia. The size of the market was simply too small. During my nearly two years as product manager, we never discussed or studied the ophthalmology market. Our focus was entirely on the human knee and racehorses.

So, what was it then that ultimately shifted the focus to ophthalmology? There are different explanations to this. A couple of them are held by Bengt Ågerup, who was employed at the Diagnostics Division of Pharmacia in 1975, was later recruited to the Department for Explorative Medicine at the Pharmaceuticals Division, and was ultimately appointed Chief Scientific Officer (CSO) at Pharmacia Ophthalmics in 1980. We will return to Bengt Ågerup several times in this book.

In his autobiography (2011), Endre Balazs accounts for the discovery of Healon’s usefulness in lens transplantation. His version is not entirely similar to that of Ågerup. Eye physicians David Miller and Robert Stegmann are two other central figures to have given accounts of how the discovery transpired, describing how they revolutionized the technique involved in implanting artificial lenses with the help of Healon.

**The mystical letter - who wrote it, when and to whom?**

A recurrent element in different accounts on how Pharmacia discovered the cataract surgery market is a letter containing a request for Healon syringes. However, there are different views on when the letter was written, who wrote it and to whom it was addressed. In a magazine interview with Bengt Ågerup in January, 2011 (Filter, no. 19) the sender of the letter is said to be the Boston eye surgeon David Miller. In the letter Miller asks for syringes with hyaluronic acid to be used in connection with implantation of intraocular lenses into eyes after cataract removal. According to the interview in Filter the letter was sent in 1978 and addressed directly to Bengt Ågerup:

“After having read David Miller’s letter, Ågerup decided that hyaluronic acid was one of the areas that Pharmacia should focus on.”

In yet an earlier interview (Kemisk Tidsskrift, 2001) and in conversations with me during the spring of 2012, Ågerup refers to an appraisal of ongoing research projects at the Pharmaceuticals Division that he performed at the beginning of 1978, at the request of the CEO of Pharmacia AB, Birger Lövgren. In conjunction with this evaluation, Ågerup discovered a request for Healon syringes made by the
aforementioned David Miller. Miller’s intention was to use hyaluronic acid to protect the corneal endothelium during intraocular lens implantation. The subsequent follow-up on Miller’s request resulted in the discovery of the usefulness of Healon in connection with cataract surgery, thereby turning near failure of the entire project into a success.

The fact that Pharmacia’s discovery of the ophthalmology market was preceded by various initiatives and extensive contacts between different actors is clear both from Endre Balazs’ autobiography and from interviews with David Miller as well as his colleague Robert Stegmann.

In his autobiography (Balazs, 2011), Endre Balazs points out that the protective properties of Healon during lens replacement or corneal transplantation were known already during the mid 1970’s. To confirm this, he refers to an article by his colleague Jens Edmund, professor and head of the Department of Ophthalmology at the University of Copenhagen. At the time the article was written, lens replacement was not commonplace among ophthalmologists. “Then something unexpected happened”, Balazs writes:

“The implantation of plastic lenses, used to replace cataractous lenses in the aging human eye, was becoming more and more popular. In the U.S. this process was used by more and more ophthalmologists in Florida and California than in other parts of the country. The reason for the difference was the population, with these two states having many more retirees.”

In the autumn of 1976, according to the autobiography, Balazs received a telephone call from David Miller, whom he had come to know in the 1960’s when they worked together at the Retina Foundation in Boston. At the time, Miller was head of the Ophthalmology Department at Beth Israel Hospital, an affiliate of Harvard Medical School. Miller told Balazs that he had performed his first intraocular lens transplant and that the implant must have touched a large portion of the corneal endothelium during surgery because the cornea remained edematous for about a month.

Miller asked Balazs to send Healon in order to put its protective properties to the test on rabbits as well as humans. At this, Balazs immediately forwarded the request to Pharmacia. Miller received Healon from Pharmacia and tested it successfully in intraocular lens implantation in humans. He also started studies on the effects of Healon on rabbit eyes. The results of these studies were published as early as in December 1977 (Ophthalmic Surgery, 1977).

Of key importance for the future success of Healon on the eye surgery market was David Miller’s cooperation with Robert Stegmann, chief of the Ophthalmology Department of Garankua Hospital in Pretoria, who happened to be a visiting researcher.
at Miller’s laboratory during 1976-77. Due to unusual circumstances in the South African health care system, it was possible for Stegmann to design a clinical trial, carried out during 1978, where the effects of Healon could be evaluated on patients with advanced cataracts on both eyes. The results of these early studies of Healon in connection with cataract surgery were summarized in a lecture entitled “Viscosurgery and the use of Na-hyaluronate in intraocular lens implantations”, written by Miller, Stegmann and Balazs, and presented by Stegmann at the International Congress and First Film Festival on Intraocular Implantation in Cannes, May 1979.

Balazs concludes:

“Miller and Stegmann’s enthusiastic interest in using Healon during plastic lens implantation and later in other surgical procedures in the anterior chamber was a great contribution to the development of the therapeutic use of hyaluronan in the eye.”

A more detailed presentation of Miller’s and Stegmann’s early experiences with Healon can be found in an interview published under the heading “Early days of Healon” in EuroTimes, the journal of ESCR, the European Society of Cataract and Refractive Surgeons (February, 2007).

David Miller recalls:

“The arrival of IOLs (intraocular lenses) created a demand for something to protect the endothelium. You had to slip the IOL into a moderately large incision. When you made the incision, the eye would collapse and vitreous would flow out. It was really very difficult not to brush the back of the cornea, and the plastic the IOLs were made of was hydrophobic, so they tended to attract the endothelial cells. This was a prescription for disaster and many surgeons had a lot of trouble. It was clear we needed a lubricant.”

This is when David Miller came to think of his former colleague at Retina Foundation, Endre Balazs, whose work with Healon for primarily orthopedic use he was familiar with. Miller thought that the product might be useful in ophthalmology as well, and recommended Robert Stegmann to visit Balazs in New York. According to Stegmann, Balazs had little enthusiasm for the idea of using hyaluronic acid in cataract surgery, but finally gave Stegmann six ampoules (“… after a couple of beers I twisted his arm in a pub to give me six ampoules.”). The ampoules were used in rabbit surgery, and the results were described by Stegmann as absolutely remarkable.

According to Robert Stegmann, in the same interview, the introduction of Healon came at a critical time in the history of IOLs. There was a moratorium on IOLs in two states in USA, and an imminent threat that they could even have been banned nationally.
“IOLs could have died. There was a tremendous amount of resistance to IOLs. All three established chairs of ophthalmology in Europe had condemned these things as tools of the devil.”

Stegmann was convinced that the controlled clinical trial conducted in South Africa, the results of which were presented at the aforementioned conference in Cannes in May 1979, had an eye-opening effect on Pharmacia with respect to the cataract surgery market. The trial, which included 40 eyes of 20 patients, showed that the corneal endothelial cell loss was only nine percent in the Healon group, compared to 45 percent in the classic air bubble group.

“These results were extremely well received and things went from strength to strength after that. From that time on there was money to develop new important designs of lenses and improved surgical techniques. Without Healon you could never have thought about putting an intraocular lens in the bag with a collapsed chamber; there was no way you could ever have made a circular capsulorhexis.”

When talking to Robert Stegmann over the phone in March 2015, he refers to Healon as “the most significant breakthrough in eye surgery in the last 100 years.”

**Pharmacia’s late realization of Healon’s potential**

We return to the mystical letter, which seems to have played an important role in Healon’s entry onto the cataract market, but which initially received very little attention at Pharmacia. What actually took place involving this letter? As mentioned, Miller received access to Healon already by the end of 1976, according to Balazs. When I ask Endre Balazs about the letter in September 2013, he maintains the information given in his autobiography, namely, that it was he and not Miller who sent the letter to Pharmacia, which contained an order for syringes to be sent to David Miller. Balazs does not remember to whom he addressed the letter at Pharmacia, but it was certainly not Bengt Ågerup. Their paths would not cross but yet for another few years.

With regard to Pharmacia’s seemingly slow response to Healon’s potential on the cataract market, a plausible scenario, according to Balazs, is that someone at Pharmacia received his letter and delivered syringes to David Miller in late 1976 without knowing or reflecting over what the syringes were to be used for. It was not until Miller and Stegmann had completed animal testing and undertaken clinical trials on patients in South Africa in 1978 that Pharmacia began to realize the potential on the eye market. Balazs claims that he and his wife Janet were actively involved in supporting
Stegmann’s clinical trials, even traveling to South Africa at one point in order to deliver a special microscope that was needed.

When in April 2013 I asked Erik Danielsson, Pharmacia’s CEO from 1984 to 1990, about when he and his colleagues started to discuss Healon’s possibility on the cataract market, he recalls a dinner organized by Karl Arfors sometimes around the end of 1978, or beginning of 1979. Arfors, who at that time was head of the Department of Experimental Medicine at Pharmacia, had invited some of his colleagues at the Pharmaceuticals Division to dinner, the purpose of which was to identify possible areas of application for Healon. At the time, Danielsson was, among other things, responsible for the marketing of Healon on the racehorse market. One of Danielsson’s memories from the evening was an activity arranged by Arfors in which the dinner guests were asked to roll a specially prepared die to determine which application to focus on. On the side that came up after the first roll was “Eyes”. A closer examination of the die revealed that “Eyes” was written on all six sides.

When talking to Karl Arfors about Healon in September 2014, he confirms Danielsson’s story about the die, but like Danielsson he has difficulties remembering exactly when the dinner took place. Arfors also confirms that a letter containing a request for Healon syringes to be delivered to David Miller was found at his department, possibly by Bengt Ågerup. When the importance of the request was realized, Arfors ordered Ågerup’s colleague and office mate Ove Wik to visit Miller in Boston and learn about his experiences with Healon.

Wik was a doctoral student at the Department of Medical and Physiological Chemistry at Uppsala University, supervised by Torvard Laurent. In 1979, he presented his doctoral thesis “Physiochemical studies on hyaluronate”, and then became actively involved in Pharmacia’s developmental work on Healon for more than 20 years. Ove Wik remembers the visit to Miller’s lab at Beth Israel Hospital in Boston, and believes he was the first person from Pharmacia to meet David Miller. Like Arfors he has problems recalling exactly when the visit took place, but thinks it was during the autumn of 1978.

About the time I began to feel like “enough is enough” with respect to how Pharmacia indeed discovered Healon’s eye market potential, I noticed that David Miller has a personal website10. I was instantly drawn to a portion entitled “The Healon Story”, where the following can be read:

”Miller understood that a viscous bio-acceptable lubricant would solve the problem. ….This realization prompted him to contact Pharmacia, a Swedish drug company who

10 http://www.davidmillermd.org/MILLERMD/BIO_SKETCH.html

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was synthesizing the material from rooster combs and selling injectable hyaluronic acid (called Healon) for the treatment of arthritis in horses. His timing could not have been more fortuitous. Hyaluronic acid sales had plummeted to the point that the company decided to close the factory. When Miller approached Pharmacia, he had already shown, through published animal experiments, that the substance was safe for eye surgery. He had also used it in human cataract surgery and shown that it prevented injury to the cells on the back of the cornea. Thus, Pharmacia postponed the closing of their factory and agreed to support a large surgical trial to verify his findings. The trial was performed by Miller’s colleague and first student, Prof. Robert Stegmann of Pretoria, South Africa. The trial proved the usefulness of hyaluronic acid and he and Stegmann were sent around the world to teach the technique. … Naturally, the huge increase in use of Healon allowed Pharmacia to grow almost exponentially. Out of gratitude and respect, Pharmacia proposed the establishment of an endowed chair in ophthalmology at Harvard for Miller. Unhappily, academic rivalry for the chair raised its ugly head and so Pharmacia, not interested in being involved in the controversy, withdrew the offer.”

In addition to claiming that he was the one who ordered the Healon syringes from Pharmacia, Miller’s story contains a few truly sensational accounts. One of which is that his order caused Pharmacia to delay the upcoming closure of a Healon production facility, which is not quite correct. Yet another revelation is Miller’s thwarted endowed chair at Harvard.

Before I finally leave my explorations of the mystical letter, I bring up the topic during an email exchange with Bengt Ågerup in October, 2014. ”It (the letter) was addressed to the 'Director of Research at Pharmacia’”, he recalls. Well, whoever it was that wrote the letter, when and to whom, the fact remains that a chain of events set in motion during the autumn of 1976 enabled the transformation of Healon from ugly duckling to swan.

### Medical device instead of drug - a discovery of crucial importance

Once Pharmacia became aware of Healon’s potential on the ophthalmology market, things moved quickly. A major contribution to the rapid development was the revelation that Healon, when used in eye surgery, could be classified in the U.S. as a surgical device, and not as a drug. According to my successor as product manager for Healon, Gunnar Vikström, this was an insight gained thanks to Pharmacia’s participation in the Second U.S. Intraocular Lens Symposium in Los Angeles in April, 1979. Gunnar recalls:
“Accompanied by colleague Wes Domareki from our U.S. subsidiary, I took a stroll around the exhibition to survey things, mostly in terms of identifying which competitors we would encounter on the market. At some point, we came to a booth explaining the use of methylcellulose in ICL surgery. We asked immediately how an undocumented, rather crude substance was allowed for delicate eye surgery. The answer we received was that the product was approved for use as a medical device rather than a pharmaceutical. I proposed that we began looking into the possibility of doing the same with Healon, thereby avoiding the 6-7 years of expected waiting for approval as a pharmaceutical drug. We asked a colleague at the American subsidiary by the name of Bill Murphy to examine the matter further. He got back to us within a week, confirming that it was possible to register Healon as a medical device. Marketing of the product would be allowed within three months of the so-called 510(k) application having been submitted to FDA.”

In the autumn of 1979 the 510(k) authorization to market Healon was granted, resulting in a veritable breakthrough for the product at the American Academy of Ophthalmology congress in San Francisco in November 1979. Two questions frequently asked by the eye surgeons at that congress were, according to Gunnar Vikström: “Where can I get hold of Healon?” and “where can I buy Pharmacia shares?”
CHAPTER 10: Healon’s development according to Pharmacia’s annual reports

Pharmacia’s annual reports from the end of the 1970’s and onward give an accurate overall picture of the exceptionally successful development of Healon. The product is first mentioned in the 1976 annual report, during the launch of Healonid Vet. on the French veterinary market. Moreover, the new production plant for Healon, mentioned in Chapter 6, is referred to as one of the major investments in Uppsala during the year. Under the headline “Prospects for 1977,” the following is stated: “The launch of Healon Vet. for joint disorders on horses will continue in several countries.” As we know from Chapter 6, the only such success that was realized in 1977 was the launch of the product on the Australian veterinary market at the end of the year.

1979

Nothing is mentioned about Healon in the annual reports of 1977 and 1978. In the annual report of 1979, there is an article about the isolation and purification of natrium hyaluronate from rooster combs. The article describes efforts by the Pharmaceuticals Division in investigating the possibility of Healon use for various types of joint problems in humans. The product is also found to be useful for eye surgery, and has been approved as a surgical device for the same in the U.S. and Canada by the end of 1979. There is a proud photograph in the report from a symposium on Healon at Pharmacia in Uppsala in October 1979. Pharmacia’s total sales in 1979 amount to approx. 175 mUS$.

1980

In the annual report of 1980, newly appointed Group CEO, Gunnar Wessman uses Healon as an example of “multi-marketing”. Under the headline “New, important business area” the launching of Healon on the U.S. market in April 1980 is mentioned. Report readers are informed that Healon, as a device for certain types of eye surgery, is believed to quickly become one of the most important products of the pharmaceutical division. A full page in length, with the headline “Healon, a product for the global market”, a detailed presentation is given regarding the technique involved when using Healon in connection with lens transplantation.
1981

The annual report of 1981 makes note that total sales of the Group (which is called Fortia until 1983, when the original company name, Pharmacia, is reestablished) exceeds 1 billion SEK for the first time (approx. 200 mUS$), and that the Pharmaceutical Group, of which Erik Danielsson is new CEO, and to which Healon belongs, accounts for almost 50 percent of total sales. Healon is, merely one year after its launch in the USA and Canada, the fourth largest product of the unit. In order to best take advantage of the business opportunities that exist on the eye surgery market, a new business unit is created, Pharmacia Ophthalmics. During 1981, Healon has been launched in Spain and Switzerland, and the countries that follow during 1982 are, among others, England, West Germany, France and Scandinavia. Production capacity for Healon has been considerably increased and new products for the ophthalmology market are expected to be developed through internal R & D as well as through acquisition and cooperation.

1982

From the annual report of 1982 we learn that “Ophthalmic surgery is developing strongly in the United States and a number of other countries, creating a rapidly expanding market for Healon. More than 400,000 lens transplantations were performed in the U.S. during the year.” It is also mentioned that Pharmacia has acquired the Dutch company Medical Workshop B.V., which is a leading manufacturer of intraocular lenses. The company also manufactures disposable instruments for ophthalmic surgery. The business unit (i.e. Pharmacia Ophthalmics) expects a substantial synergistic effect in marketing Healon and intraocular lenses together. Total sales of Healon during 1982 amount to approx. 20 mUS$ and the product is referred to as “one of the Group’s best-selling products”.

1983

According to the annual report of 1983, total sales of the Pharmaceutical Group amount to 133 mUS$, which is more than twice that of 1981. The reason stated is: ”... the exceptionally rapid expansion of Healon in the U.S.” Total sales of Pharmacia Ophthalmics in 1983, most of which is Healon and a small part IOLs, amount to 43 mUS$. This means that Healon has now become Pharmacia’s largest product. This has been achieved despite the fact that production capacity is not yet fully developed, and the product has still not been launched on important markets such as Japan. The U.S. market continues to dominate. The report also mentions that the expected number of
lens transplantations to be performed during 1984 is 750,000, of which 600,000 in the U.S.

The 1983 annual report contains an article with the headline “The eye surgery market – a breakthrough” where Endre Balazs’ contribution to Pharmacia’s success with Healon on the eye surgery market is presented as follows:

“The development and use of Healon originates from the work of the Hungarian born professor Endre Balazs. He approached Pharmacia in 1972 with his ideas of using hyaluronic acid as an aid in connection with, among other things, eye surgery.”

In the 1983 annual report, the existence of competing products on the eye surgery market is mentioned for the first time.

1984

During 1984, Erik Danielsson, who was product group manager when Healon was launched on the French racehorse market in 1976, takes over the position as CEO of Pharmacia from Gunnar Wessman, who becomes new chairman of the board. Healon has consolidated its position as Pharmacia's biggest product and Pharmacia Ophthalmics has increased sales from 40 to 62 mUS$ (+ 55 %). This represents almost one fifth of Pharmacia’s total sales, which amount to 345 mUS$. The report concludes:

”Healon is well established in all major markets except Japan, where the application for registration was not submitted until 1984……Healon may be considered to have 96 percent of the US market for viscoelastic products, compared with barely 1 percent for a recently introduced, competing product. Other, old viscous products account for 3 percent of the market.”

A photo in the report confirms that CEO of Pharmacia Ophthalmics, Hans Åkerblom, has left his post during 1983. Instead, he has joined Group management, acting as Vice President, responsible for human resources and company culture. New CEO of Pharmacia Ophthalmics is Jan-Erik Engkvist, recruited to Pharmacia from American Cyanamid in 1982. The appointment of Engkvist as CEO resulted in major changes in the management of Pharmacia Ophthalmics during 1984, which I will return to below.
1985

The Healon success story continues. Total sales of the Ophthalmics Division\textsuperscript{11} amount to 77 mUS$, meaning an increase of 24 percent as compared to 1984. The CEO of Pharmacia, Erik Danielsson, gives the shareholders the following message in the annual report of 1985, the year Volvo became principal owner of Pharmacia:

"Pharmacia is, and will for the foreseeable future, be the leading company in the field of ophthalmological viscosurgery…The prospect of developing HA additionally into products outside the present area of application – ophthalmic surgery – is also highly attractive. A number of patent applications were filed during the year and we are convinced that Pharmacia has a substantial technological lead in this field."

The annual report gives an extensive presentation of the international expansion of Healon. The year marks a break-through for Healon in Europe, thanks to a marked increase in the number of intraocular lens implants. The U.S. remains the dominant market despite increasing competition, and sales continue to increase both in volume and value.

For the first time, competitors on the ophthalmology market are mentioned by name. In the U.S., a company called Frigitronics Inc. markets a low-molecular fraction of hyaluronic acid through its subsidiary Precision-Cosmet Company Inc. These companies, closely linked to a previous colleague of Endre Balazs at Retina Foundation, Dr. David Swann, will be returned to below. Precision-Cosmet Company is also a competitor on the intraocular lens market. Other competitors include Iolab, Cilco and American Medical Optics (AMO).

Mentioned as one of four major business events during the year, a five-year research agreement is signed with Biomatrix Inc. concerning research in the hyaluronic acid segment for ophthalmic applications. Biomatrix Inc. is a company started by Endre Balazs and his wife Janet Denlinger in 1981. A closer presentation of the company and the circumstances behind its creation will be given in Part III.

1986

Sales of Pharmacia Ophthalmics AB amount to 104 mUS$ in 1986, an increase of 35 percent, in spite of a declining dollar rate. Important business events during 1986 include the introduction of Healon on the Japanese market and the acquisition of Intermedics Intraocular Inc., based in Pasadena, California. In connection with this

\textsuperscript{11} The name of the company, or business unit, changes from year to year
acquisition, Pharmacia relocates its operations in the ophthalmic sector from New Jersey to Pasadena and creates Pharmacia Intermedics Ophthalmics, a company with around 400 employees.

More than two million eye operations were estimated to have been performed around the world in 1986, and as for 1987, an even larger number is expected. Regarding competition, Precision-Cosmet Company is again mentioned, the producer of a low-molecular type of hyaluronic acid, which by now has been acquired by the U.S.-based company Iolab Corporation.

1987-88

The annual reports of 1987 and 1988 reveal that competition is becoming of increasing concern. This is especially true in the case of the American market, where the principal competitors are Amvisc®, the low-molecular type of hyaluronic acid marketed by Iolab, and produced by Med-Chem Inc., and Viscoat®, produced by Alcon-Coopervision-Cilco. In Japan, the principal competitor is Opegan®, by Santen.

Despite stiff competition, total sales of the Ophthalmics Group increased from 160 mUS$ in 1987 to 190 mUS$ in 1988. This was attributed to the steady growth of ophthalmic operations in many countries. The total number of operations on a worldwide basis, of which cataract extraction is the most common, is estimated to three million, of which almost 50 percent were performed in the United States.

1989

The 1989 annual report makes clear that the U.S. market is still the largest of the Ophthalmics Group, but its dominance has started to decrease. Of total sales in 1989, which amounted to 205 mUS$ (up eight per cent from 1988) the U.S. and Canada account for 47 percent, Western Europe 34 percent, and Japan 13 percent. While the ophthalmic market in the U.S. has almost ceased to increase, substantial increase continues on most other markets, particularly in Japan, where the number of cataract operations has gone from 30,000 to 170,000 in three years.

A major event reported in the 1989 annual report is Pharmacia winning the first round of a lawsuit against Med-Chem for infringement of a patent covering Healon. The outcome of the trial is reported as “...an injunction enjoining MedChem from producing, distributing or selling Amvisc in the U.S.” Amvisc was, as mentioned above, a principal competitor of Healon on the U.S. market, and chairman and CEO of
MedChem at this stage, and also one of its founders, was Dr. David Swann, former colleague of Endre Balazs at Retina Foundation.

1990-98

The annual report of 1991 reports that Pharmacia has withdrawn the lawsuit for patent infringement filed against MedChem, and a settlement has been reached. The result of the settlement, according to “The Gray Sheet”\(^\text{12}\), was MedChem paying Pharmacia 12.2 mUS$, in order to be allowed to continue the manufacturing of Amvisc for sale on the U.S. market. This was done so through its exclusive distributor Iolab, which was then forced to pay royalties to Pharmacia based on product sales. This dispute, together with other conflicts related to Healon and other hyaluronic-acid based products, will be returned to in part VI of this book.

Increased competition in an increasingly saturated market resulted in sales of Healon and IOLs flattening out at the beginning of the 1990’s, and beginning to decline by the mid 1990’s. The “all-time high” for Healon was reached in 1993 when total sales accounted for 1.67 billion SEK (≈ 214 mUS$). This can be compared with sales of 1.1 billion (≈ 138 mUS$) in 1998, which is the last year the sales figure of Healon is separately indicated in the annual reports of Pharmacia & Upjohn.

Organizational changes at Pharmacia during the 1990’s, including the merger with Kabi in 1990, and later with Upjohn in 1995, in combination with declining sales, saw the relative importance of Healon and IOL’s decrease. In the 1992 annual report of Kabi Pharmacia, Healon is reported as the second largest product of the company, after Genotropin. The IOL’s are listed as the eight biggest product. In 1997, Healon is bumped to number ten on the list, and in 1998, number eleven of Pharmacia & Upjohn’s products. In ninth place on the 1997 list is a product, which in 1998 had managed to climb and become the second biggest product at Pharmacia & Upjohn. This product, which can be seen as a spin-off from Healon, and to which we will return in Part IV, is Xalatan.

\(^{12}\) Elsevier Business Intelligence (1993)
Healon today

In 2003, Pharmacia Corp., which was the new name of the company after Pharmacia & Upjohn’s merger with Monsanto in 2000, was acquired by Pfizer. In 2004 was announced that AMO (Advanced Medical Optics Inc.) had purchased Pfizer Inc.’s surgical ophthalmology business for 450 mUS$ in cash. AMO, based in Santa Ana, California, had split from Allergan in 2002, a company we will return to in part V, when discussing the role of hyaluronic acid on the facial aesthetics market. AMO’s acquisition included the Healon line of viscoelastic products, the CeeOn and Tecnis IOL’s, and the so-called Baerveldt glaucoma shunt, products which according to Pfizer had generated sales of approximately 150 mUS$ in 2003\textsuperscript{13}. The acquisition also included manufacturing and R&D facilities in Groningen, Netherlands; Bangalore, India; and Uppsala, Sweden. This meant that the manufacturing of Healon would continue to take place in the facilities in Uppsala, originally built in the late 1970’s.

At the beginning of 2015, production of Healon still takes place at Fyrislund, Uppsala, but the “A” in AMO now stands for “Abbott” after Abbott Laboratories’ acquisition of the company in 2009. The production of Healon employs approximately 150 people and the rooster combs, on which the production is still based, come from the rooster farm outside Uppsala started more than 30 years ago. The daily number of operations in which Healon is used amounts to 8,000 (= approx. 3 million per year) worldwide, according to AMO. The main difference now, when compared to the 1980’s, is that Healon is no longer the only hyaluronic acid-based surgical device on the market. Naturally, that the price per syringe has decreased considerably.

\textsuperscript{13} This can be compared with 1993, when the total turnover of the Ophthalmics Group was twice as high, approx. 300 mUS$.
CHAPTER 11: Four key players at Pharmacia Ophthalmics

The success of a specific product or company is frequently explained by the actions of a specific person. Consequently, Microsoft’s success is attributed to Bill Gates, Apple’s success to Steve Jobs, and Chanel No. 5’s to Coco Chanel. Others claim that the success of a company or product very seldom, if ever, can be attributed to a single person. Rather, it emerges as a result of well-functioning teamwork, or a combination of different factors. For example, good teamwork applied to a superb innovation launched on the market at exactly the right time. In order for all three factors to successfully interact, a fourth factor should also be at hand, namely that thing some call luck, others chance.

The words ”luck”, “chance”, and ”timing” have often been used to describe Pharmacia’s success with Healon on the cataract market. Healon became a self-playing piano once its market presence had been established. Who was in charge at Pharmacia during the time was seemingly unimportant, as failure would have been nearly impossible. However, there are those who would argue against such sentiment. I happen to believe that Healon’s success can be attributed to a number of key individuals, who made decisive decisions at specific phases during the process.

As described at the beginning of this chapter, three people outside Pharmacia can be said to have played crucial roles in the discovery of the usefulness of Healon in connection with cataract surgery, namely Endre Balazs, David Miller and Robert Stegmann. Four individuals within Pharmacia that were deeply involved in, and had a strong influence on the creation and development of Pharmacia Ophthalmics, were Erik Danielsson, CEO of Pharmacia 1984-90, Hans Åkerblom, CEO of Pharmacia Ophthalmics 1980-83, Bengt Ågerup, CSO of the same company 1980-84 and Jan-Erik Engkvist, CEO of Pharmacia Ophthalmics 1983-90. All four of them have shared their memories and experiences from working with Healon in different media sources. I have also had the opportunity to have personal conversations with all four of them while writing this book. The following is an attempt to summarize their stories.

**Erik Danielsson, CEO of Pharmacia 1984-1990**

Erik Danielsson likely has the longest single relationship both with Healon as a product and with its inventor, Endre Balazs. Danielsson was employed at Pharmacia in 1970, directly after having finished his studies at Uppsala University. In 1976, he was given responsibility to introduce Healon onto the market. By this point, he had advanced up the ranks and was group product manager for Pharmacia’s dextran products.
Danielsson had long been considered a Healon ally, together with research manager Harry Hint. Given the significant difficulties seen by Healon from the start, many within Pharmacia were of the opinion that the venture should be ended entirely. Danielsson and Hint struggled against a growing force of opposition and readily explained that the future was bright regarding Healon. The future would eventually prove to be brighter than anyone had dared to dream.

At the time of Healon’s April, 1980 release in the U.S., Erik Danielsson had continued to advance within Pharmacia. His role at the time was manager for the company’s largest entity, the Pharmaceuticals Division. Danielsson was in complete control of Healon and made two key strategic decisions that lead to great success. First, he created and designated a new business area specifically for Healon, the Ophthalmics Division. Second, he appointed Hans Åkerblom chief of the new division. Åkerblom was unknown within business circles at Pharmacia, as he had previously worked at the department for human resources.

As manager for the Pharmaceuticals Division, Danielsson could eagerly follow Healon’s development on the U.S. market. From its introduction and until the end of 1983, Healon grew steadily, much to Danielsson’s delight. By 1983, Healon had become Pharmacia’s largest product. Pleased with the work of Hans Åkerblom, Danielsson recommended him as a new member of Pharmacia’s board of directors. Åkerblom accepted and was replaced as CEO of Pharmacia Ophthalmics by Jan-Erik Engkvist. Danielsson was also involved in the decisions that resulted in Bengt Ågerup’s departure from Pharmacia (see below), even if his own actions were indirect.

Of utmost importance, Erik Danielsson was in charge of trying to maintain a favourable business relationship with Healon’s inventor, Endre Balazs. According to Balazs himself, part of this responsibility was to ensure further development of Healon on the eye market at the expense of opportunities on the human osteoarthritis market. Danielsson was in a difficult position. In short, he was obliged to further Healon’s success on the eye market, while at the same time paying lip service to Balazs’ intent with respect to Healon’s potential as an arthritis medicine. To this end, Danielsson was eager to support Balazs and Balazs’ company Biomatrix without specifically directing much of it to the arthritis market. The balancing act resulted in large contributions from Pharmacia to Biomatrix during the company’s first ten years of operation in the form of research grants and stock acquisitions. More on this will follow in Part III.

**Hans Åkerblom, CEO of Pharmacia Ophthalmics 1980-1983**

Hans Åkerblom was the CEO of Pharmacia Ophthalmics from the initiation of the company in the autumn of 1980 until the autumn of 1983, at which point he was invited
to join the Group Management Team, responsible for personnel and business culture. He remained in this position until he left Pharmacia in 1985.

Åkerblom was employed at Pharmacia at the beginning of the 1970’s, and worked initially at the human resources department. He had a strong interest in management related matters and had, during his days as a student at Uppsala University, developed a management tool, LOTS®, together with a fellow student, Åke Strömberg. Strömberg would also later work at Pharmacia. Hans Åkerblom left Pharmacia in 1985 mainly to manage and take full advantage of the successful introduction of LOTS on both the national and international market.

The strategic review that preceded the start of Pharmacia Ophthalmics

During the autumn of 1979, Hans Åkerblom was asked by Group CEO Gunnar Wessman, who knew of Åkerblom’s role in the development of LOTS, to lead a strategic review of Pharmacia. A group of strategic reviewers, including members of the Group management team, as well as the CEO of each subsidiary, met on various occasions during the first half of 1980. An important conclusion arrived at by the strategy group was that Pharmacia should switch from production oriented to a more customer oriented company. It was also suggested that Healon be assigned a business unit of its own within the pharmaceutical division, where Erik Danielsson had recently become division head. During the summer of 1980, Erik Danielsson asked Hans Åkerblom to take on the role as head of the new Healon business unit. After a final meeting with the strategy group he accepted.

The successful start of Pharmacia Ophthalmics, as told by Hans Åkerblom in 1988

After a meeting with Hans Åkerblom in April 2013, where we discussed memories and experiences of Healon and Pharmacia Ophthalmics, he sent me a video tape recorded in 1988. The primary purpose of the video tape was to promote LOTS, but the case on which the presentation is based is Pharmacia Ophthalmics. In short, his presentation highlights the following:

- The importance of defining relevant criteria from which the ideal customer group for a product can be identified. In the case of Healon, this resulted in the identification of the ophthalmologist as the ideal customer from a list which originally contained 16 possible applications.
- Identification of the key customer group should be followed by identifying the purpose of a business activity. In the case of Pharmacia Ophthalmics the following purpose was established: “... to develop, produce, market and
sell products and other solutions to the ophthalmologist when he is diagnosing, treating and following up his patients.”

- Next step is to formulate a clear strategy, which in the case of Healon became: “Pharmacia Ophthalmics, a serious and reliable partner with Healon and other innovative products that facilitate eye surgery.”

- Based on purpose and strategy, both long and short-term objectives should be established. For Pharmacia Ophthalmics, a long-term objective of sales exceeding 80 million US$ within five years was decided. This was an ambitious objective as Pharmacia’s total sales amounted to 150 million US$ in 1980. Most of the short-term objectives pertained to gradual success on the American market, the first to be pursued.

- Given the long- and short-term objectives decided upon, different activities must be identified in order for the objectives to be met. One such activity in the case of Pharmacia Ophthalmics was the establishment of a rooster farm near the head office in Uppsala. Another important action was organizing expert lead symposia where eye physicians could practice lens implantation with the help of Healon. A third activity was the 1982 acquisition of a Dutch company, Medical Workshop B.V., a manufacturer of intraocular lenses. As a result, Pharmacia could offer eye physicians a complete package for cataract surgery.

- A prerequisite for the successful implementation of a business strategy is access to relevant competence which, according to Åkerblom, was a key factor in Pharmacia Ophthalmics’ success with Healon. By this he refers both to the people that worked with him at the head office, and the people at the subsidiaries, particularly the one in USA. This resulted in a team spirit where all involved spoke the same language, both literally and figuratively.

- The three final components in Åkerblom’s LOTS-based model for successful implementation of a business strategy are communication, critical events and follow-up. The excellent team spirit created within Pharmacia Ophthalmics greatly benefited communication between the head office and the foreign subsidiaries. The head office was largely focused on strategy and long-term objectives while the subsidiaries were responsible for short-term objectives and the activities that were necessary to realize them. An important component in the process was identifying and reporting which critical events were crucial for success. Among such events were: adequate supplies of rooster combs, sales progress on key markets, and obtaining the proper product approval according to the timeline. Follow-up was deemed most important to evaluate headway on short-term objectives. In the case of Healon, short term objectives were constantly being met above and beyond expectations, leading to continual re-evaluation of long term objectives.
The video presentation ends with a speaker voice informing that Pharmacia Ophthalmics’ turnover in 1987 exceeded 1 billion SEK (approx. 150 mUS$) and that the business unit accounted for 40 per cent of Pharmacia’s profit that year.

Some complementary thoughts, 25 years later

When discussing Healon and Pharmacia Ophthalmics in April 2013, Hans Åkerblom points to the following turning points and key decisions that enabled Pharmacia’s success with Healon and, with time, even that of Xalatan.

- The IOMS, Intraocular Microsurgical Seminars, which were mentioned in the video recording above. The three eye surgeons who ran these seminars were the aforementioned David Miller and Robert Stegmann, together with Bo Philipson from Sweden.
- The creation of the company’s own rooster farm. By saying “yes” to this investment, Pharmacia’s board of directors likely made the most profitable decision in the history of the company, according to Hans Åkerblom.
- The acquisition, in 1982, of Medical Workshop B.V., manufacturer of intraocular lenses, which enabled Pharmacia Ophthalmics to diversify its business and to offer the eye surgeons a complete “package” for cataract surgery.
- The 1983 acquisition of a patent for future “blockbuster” Xalatan, from Columbia University and the researcher behind the patent, Lazlo Bitó, who was a colleague of Endre Balazs. The acquisition, which was seen as a long-term, strategic investment, was made by Hans Åkerblom together with his closest ally at Pharmacia Ophthalmics, CSO Bengt Ågerup.
- The development of a customer oriented marketing strategy based on the vision “one out of five in eighty-five”. The positioning arrived at through this vision was: "Healon from Pharmacia Ophthalmics facilitates eye surgery by maintaining space, protecting tissues and you can gently maneuver tissues into desired position. Pharmacia Ophthalmics is a serious and reliable partner."

The vision “one out of five in eighty-five” was, according to Jan Jajke, a former employee at Pharmacia Ophthalmics, launched by Hans Åkerblom in connection with the World Ophthalmology Congress in 1980, at which time Pharmacia Ophthalmics was practically unknown. Jajke means that the vision was surpassed: "We were one out of four in eighty-four". Åkerblom claims they were even more successful: "We were one out of three in eighty-three".

When interviewing former employees of Pharmacia Ophthalmics both in Sweden and in the U.S. during the autumn of 2013, they confirm most of the narrative told by Hans
Åkerblom: Yes, there was a clearly defined vision that we all were aware of and believed in, and yes, we used a much more systematic approach than we were used to. Also, the IOM-seminars was a brilliant idea that gave us access to customers on the ophthalmology market in a very time efficient way, disabling the usual top-down approach. Instead, there was lots of listening and mutual respect.

However, Hans Åkerblom’s description regarding the decision to pursue the ophthalmology market has not been confirmed. The decision was not based on a systematic plan to a predetermined end. By the time Åkerblom took over as CEO for Pharmacia Ophthalmics, Healon had already been introduced to a U.S. market eagerly awaiting its arrival. This was much more a case of “demand pull” than “supply push.” Demand from ophthalmologists in USA was enormous, causing the parent company in Uppsala, Sweden to struggle with the pace at which orders were being received for the first 18-24 months. It was a time marked more by determination rather than inquiry.

**Bengt Ågerup, Chief Scientific Officer of Pharmacia Ophthalmics 1980-1984**

Lots of articles and interviews have been published about Bengt Ågerup, most of which have focused on the success he has experienced with the company Q-Med and how this has affected his life. In some cases, his experiences from Pharmacia and his role in the development of Pharmacia Ophthalmics have been seen as the backdrop of his career as a successful innovator and entrepreneur.

A rather detailed presentation of Bengt Ågerup’s experiences with Pharmacia and Healon is given in the book *Svenska Miljardärer (“Swedish Billionaires”)* by Birgitta Forsberg (2012). In the book, which presents ten Swedish “self-made” billionaires, Ågerup tells of his role in the selection of Healon as a priority project at the end of the 1970’s. He also tells of his search for rooster combs throughout Europe, a problem later solved by the company starting its own rooster farm.

“We managed to introduce Healon on the U.S. market very rapidly. We claimed that Healon would reach a sales volume of 100 mUS$ within three years and have a profitability of 60-70 per cent. When this was said the total sales of the entire pharmaceutical division was 40 mUS$. It was very provocative and not very many believed in our statements. We were three, four believers who tried to calculate Healon’s potential, how many people were suffering from cataracts, and how long time was needed to teach enough eye surgeons… We did a lot of new things; a former HR-director as the head of the division, myself as head of research, and another person as head of development. It was a very good team.”
According to the book, an important lesson Bengt Ågerup learned from Healon was that price sensitivity is very low if you have a good product. The cost for producing a single dose of Healon was slightly less than 2 US$. However, Pharmacia was able to charge a price forty to fifty times higher as the product was used in conjunction with very expensive procedures.

Ågerup also tells about his active role in Pharmacia’s 1983 acquisition of the patent that later resulted in the success of Xalatan. This will be returned to in Part IV.

Shortly after the Xalatan deal with Columbia University and inventor Lázló Bitó had been signed in the autumn of 1983, Hans Åkerblom left his post as CEO at Pharmacia Ophthalmics to become a member of the Group Management Team. Changes at the top management level of Pharmacia in combination with the appointment of Jan-Erik Engkvist as new CEO of Pharmacia Ophthalmics radically changed Bengt Ågerup’s professional situation. In Forsberg’s book he describes the new management as a group of opportunists and claims that from that day all development activity at Pharmacia Ophthalmics ceased. His relationship with Engkvist is described as a power struggle between the bohemian and the reputed boss from the big company world:

“He came and run endless meetings. I said to him: Can’t you rationalize? We can’t sit for a whole day, listening to your eternal talking.”

At one point Ågerup had promised to knit scarves for his son’s football team:

“I was out of time and thought I should knit instead of attending meetings.”

Bengt Ågerup finally decided to bring his knitting bag to a meeting and started knitting. Engkvist, according to Ågerup, became more and more irritated and finally burst:

“Bengt, you are really demonstrating your lack of interest in my meeting by sitting here knitting.”

To which Bengt Ågerup responded:

“There is nothing strange about me knitting – not stranger than you wearing women’s underwear.”

Engkvist face reddened, and he did not know how to respond, according to Ågerup.

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14 When Birgitta Forsberg (the author of “Swedish Billionaires”) presented this story to Jan-Erik Engkvist, he dismissed it as nonsense. Ågerup never knitted at his meetings. However, there were rumors he had been knitting during Åkerblom’s time as CEO.
After a while Bengt Ågerup started to receive regular messages on his desk, which he interpreted as an attempt by Engkvist to gain the upper hand on him.

“These messages told me to check what had happened, and what should have happened. If you have to control this every day, you are a bit nervous.”

During 1984, Bengt Ågerup was stripped of his duties as chief of research. Instead, he was offered to continue as head of development. At a dinner one evening at the home of Pharmacia’s CEO Erik Danielsson, Ågerup, informed Danielsson that in his opinion the new head of Pharmacia Ophthalmics was the wrong person for a dynamic, development oriented company.

“The person you have put in charge is, at best, an administrator and controller. I think you should do something about it. We cannot continue the development of this company if Jan-Erik is allowed to work the way he does. If you keep Jan-Erik, I doubt that anybody in the management team will stay.”

Erik Danielsson’s response, according to Bengt Ågerup, was: “What does that mean? Is it a promise?” to which Ågerup was to have responded: "Yes!"

According to Forsberg, Danielsson does not remember the dinner, or the conversation, but does not exclude the possibility that Ågerup’s story is accurate. However, he rejects the idea that he would have taken the risk of losing the entire management team.

Ågerup kept his promise, in a way:

“I was kicked out. My ultimatum was not accepted by my boss. I had to return car keys, credit cards – everything. I think I was a threat to the success story of top management. Ambitious business leaders are good at claiming their contributions to success without having taken part very much.”

Whether Bengt Ågerup was kicked out from Pharmacia, or if he left voluntarily because he was not willing to accept the working conditions offered, can be discussed. In any case, he left Pharmacia at the end of 1984. Already in the next part of this book, part III, he re-enters on the scene as a consultant and, later on, employee of Biomatrix.

**Jan-Erik Engkvist, CEO of Pharmacia Ophthalmics 1983-1990**

Having read about and listened to Bengt Ågerup’s characterization of Jan-Erik Engkvist, I wanted to hear Engkvist’s own story. I wished to learn about his experiences at the helm of Healon and Pharmacia Ophthalmics during seven years. We met in Stockholm in November 2012. In addition to the information exchanged during that conversation, I received a fairly detailed written document from Engkvist about
his years at Pharmacia. This document can be seen as an attempt from Engkvist to contrast, or balance the image of him given by Bengt Ågerup in various interviews. So, based on these two sources, here is his story:

Jan-Erik Engkvist was recruited to Pharmacia from the pharmaceutical company American Cyanid in October 1982. His last post before joining Pharmacia was as product group marketing manager for Europe, the Middle East and Africa. He was based at the company’s head office in Wayne, New Jersey.

After having worked one year as marketing director and deputy head of Hospital Products at the Pharmaceuticals Division, Engkvist was offered to succeed Hans Åkerblom as CEO of Pharmacia Ophthalmics during the autumn of 1983. The business unit had at this stage around 25 employees and did not conduct any research on its own. Bengt Ågerup’s main task in his role as CSO was to interact with the research department at the Pharmaceuticals Division, and prioritize together with the ophthalmic unit.

Jan-Erik Engkvist did not know Bengt Ågerup before joining Pharmacia Ophthalmics, but had seen him in the corridors and at the lab. He had deducted somewhat of an opinion of Ågerup as being loud, dominating and ironic. He behaved as if he was “king” of the business unit, and it was obvious that he was very disappointed with the recruitment of Engkvist as CEO. “He won’t last long,” Bengt Ågerup was telling his colleagues at the business unit, and started to openly oppose and ridicule Engkvist’s management style and decision-making. Workers at Pharmacia Ophthalmics were either loyal to Bengt Ågerup, or kept their distance to him, as to avoid his dominance and irony, according to Engkvist. As a result, Engkvist had very few supporters when he began as CEO. But this did not scare him off. Rather, he saw it as a challenge, and started to do what he was good at: working hard and being an energetic and decision-oriented boss. Also, he more or less immediately decided to find a way to get rid of Bengt Ågerup.

During the subsequent 15 months, Jan-Erik Engkvist and Bengt Ågerup were constantly at odds. All business units had to present an annual business plan, including a budget, indicating planned activities within marketing and product development. Ågerup’s contribution to this plan was subpar, and he was very annoyed with all the documents that had to be written. Engkvist’s need for background information, and Ågerup’s unwillingness to provide this information was a source of constant conflict between the two. Another aspect which contributed to their deteriorating relationship was the successful development of Pharmacia Ophthalmics. The board of directors expressed great satisfaction with Engkvist’s work, and more and more staff members took his side in the conflict with Bengt Ågerup. In particular, the way Engkvist had
handled the patent infringement case with MedChem boosted his confidence in the eyes of his peers.

In the autumn of 1984, shortly after Erik Danielsson had become the new president of Pharmacia, Ophthalmics was upgraded to become a division of its own. In connection with this, Jan-Erik Engkvist decided to employ a new director of research. Bengt Ågerup, who up until that point had held the position of CSO, was offered the post as director of product development. Ågerup reacted very negatively to this degradation and after fruitless attempts to make Engkvist change his mind, he decided to leave the company. Engkvist summarizes:

“I put him under pressure during our 15 months together, and he had no other choice than to resign.”

Ågerup is not alone in being forced from Pharmacia Ophthalmics by Engkvist. In addition, Helen Backlund, project manager for the prostaglandin project is let go. The prostaglandin project would eventually lead to one of Pharmacia’s most successful product launches ever, Xalatan. Backlund later became Ågerup’s wife. More on this can be read in Part IV.

Jan-Erik Engkvist on Ågerup’s cessation:

“Despite it all, I felt bad for Bengt as he was forced from Pharmacia. There was nothing written in the newspapers, and no one internally publicly displayed any misgivings. No one stood up for Bengt Ågerup. His friends at Pharmacia were silent. Bengt had been dethroned as king of Pharmacia Ophthalmics and discarded. Ågerup likely had planned to retire at Pharmacia. Furthermore, he was thrown out by a ‘measly red haired administrator’. Unfortunately for Ågerup, the measly administrator became more and more successful at Pharmacia. Ågerup left Pharmacia as a loser. Angry, sad, hateful and maybe even depressed.”

Engkvist, the undisputed boss of Pharmacia Ophthalmics

The five years that followed Bengt Ågerup’s exit from Pharmacia Ophthalmics were characterized by steady growth. At the time when Engkvist assumed his role as CEO, the turnover of the division was approximately 43 mUS$. There were some 30 employees. By his departure in 1990, turnover was almost five times higher, and there were more than 1,000 employees. A large contributing factor as concerns the large number of employees was Pharmacia’s acquisition of Intermedics Intraocular Inc. in Padadena, California in 1986.
There are different opinions as concerns Engkvist’s contribution to Healon’s success. According to former Pharmacia employees in Sweden and the U.S., Engvist sat down to a fully garnished table. Healon was already the self-playing piano as described earlier. Erik Danielsson is of another opinion. According to him, Engkvist is one of the best managers he has ever worked with. Danielsson also claims that Healon’s continued success under Engkvist was a direct result of the CEO’s energetic and goal oriented work during the period.

Before Engkvist left Pharmacia in the autumn of 1990 to start a new career at IKEA, he had been appointed CEO a year earlier for Pharmacia’s Pharmaceuticals Division and later, during a brief time, first vice CEO of Kabi Pharmacia AB, and CEO for the division Kabi Pharmacia Läkemedel AB in Uppsala, Helsingborg and Malmö.
Part III: Biomatrix – a successful manifestation of frustration

Seen above is the cover of Biomatrix, Inc.’s annual report from 1998. The photo draws upon the story of Nils Holgersson, a classic Swedish tale by Nobel Laureate Selma Lagerlöf, about a boy’s journey through Sweden on the back of a goose. However, depicted on the report cover is not Nils Holgersson and his goose, but rather a young Endre Balazs perched upon a rooster. The symbolic nature of the picture makes many suggestions. The rooster was central to producing Balazs’ successful medical products, and Balazs held Sweden dearly both professionally and privately. Moreover, “The Wonderful Adventures of Nils” was a book he read during his childhood in Hungary.

When asked about the picture from the 1998 report, one of Balazs’ closest colleagues admits readily and with some embarrassment, that they were quite confused about it – “we didn’t have a clue about Nils Holgersson.”
CHAPTER 12: The creation of Biomatrix

As described in the document “Biomatrix 1981-2000, a history of success,” the company Biomatrix was the fourth step in Balazs’ 30-year research and development endeavor that aimed to develop a new method of treatment deemed “intercellular matrix therapy.” Central to the method was learning to utilize the molecular building blocks of the body’s tissue structures. This idea of taking advantage of building blocks such as collagen and hyaluronic acid originated in the late 1950’s.

The initial step in Balazs’ project was the research he supervised at The Connective Tissue Research Laboratories of the Boston Biomedical Research Institute from the mid-1950’s until 1968. The second step according to Balazs’ plan was the research development work undertaken between 1968 and 1976 at Biotrics, Inc., a small research company owned and operated by Balazs. The fruits of this labor eventually materialized in the form of NIF-NaHA (non-inflammatory fraction of Na-hyaluronate), a product ready for therapeutic use. It was licensed to Pharmacia and marketed under the name Healon. The third step materialized when Healon was introduced for ocular and veterinary purposes, as described by the events in Part I and II. This brings us to his fourth step, the creation and development of Biomatrix, Inc., a company that would achieve what Pharmacia never managed, namely the advancement and introduction of a hyaluronic acid-based product for the treatment of human osteoarthritis, Synvisc.

*Endre Balazs at a later stage of his career*
Biomatrix was started in 1981, a year after Healon had been introduced to the U.S. market for ocular use. Though Balazs was already receiving minimum royalties from Pharmacia in the order of 100,000 US$ annually, he could now expect substantially larger payments in sales-based royalties. At the age of 61, Balazs was now perfectly positioned for a comfortable retired life. If living out his days in relative luxury had not been substantially inviting, he could have, as his colleague László Bitó later chose to do (see Part IV), ventured into some new, unknown endeavor. He certainly had the financial means. However, such ideas were completely lost on Endre Balazs. Though undoubtedly satisfied with the level of success achieved by Healon for ocular purposes, as well as his own monetary gains, he was extremely disappointed. His dissatisfaction was the result of what he considered to be Pharmacia’s total lack of effort and insight when it came to the immense potential of Healon for treating human osteoarthritis. Furthermore, Balazs was convinced that Pharmacia’s failure to see Healon approved for osteoarthritis was a result of improperly designed clinical trials rather than deficiencies of the product.

Balazs decided therefore to take matters into his own hands. The 1976 license agreement between Pharmacia and Balazs’ own company, Biotrics, was limited specifically to the aforementioned NIF-NaHA. This enabled Balazs to develop new variants of hyaluronic acid at Biomatrix, with precise characteristics, specifically for treating joint ailments.
CHAPTER 13: Biomatrix’ first ten years

The founding of Biomatrix was much a family affair. Started by Endre Balazs and his wife Janet Denlinger in 1981, they were soon joined on the Board of Directors by Endre Balazs’ son, André Balazs, who became General Manager of the company’s production facility. Initially, there were some 10 employees, a few of which held PhD’s and had backgrounds within biomedical and biotechnological research. The company was first located on West 27th Street in New York City, in premises formerly occupied by a furrier, but relocated in 1983 to Ridgefield, New Jersey. The move allowed Biomatrix to set up its own laboratory and testing facility for production. Eager to achieve early results, Endre Balazs allowed Biomatrix to utilize two of his own patents, one of which would prove to be the basis of the company’s first product. The product assumed the same name as the company itself, Biomatrix®. With its unique make-up of proteins and hyaluronic acid, the product became one of the most important ingredients in a number of skin care products. Among those who reaped the subsequent success was Estée Lauder, which used the product in its highly profitable Night Repair® line, and had a two-year exclusivity. In addition, Biomatrix introduced its own line of skin care products that was marketed through companies in Europe and the United States. A more detailed presentation of Biomatrix activities on the cosmetics market, and the role of hyaluronic acid in the creation of a new product segment on the facial aesthetics market – the dermal fillers – will be given in Part V.

Recurring, fruitless negotiations with Pharmacia

During the summer of 1981, Endre Balazs met with Pharmacia’s pharmaceutical division CEO, Erik Danielsson in Villefranche-sur-Mer and Cannes. The purpose of their meetings was to discuss a proposal drafted by Balazs, who aimed to start a joint research company to pursue his ideas of chemically-modified and cross-linked hyaluronic acid for medical use. In a letter from Danielsson, dated September 15, 1981, it was stated that the parties were to meet again on September 23 in order to further discuss the venture. Also included in the letter was a proposal authored by Pharmacia, detailing their intentions regarding the extent of such cooperation. The letter also included a description of the responsibilities Pharmacia expected each party to accept. The letter established:

”WHEREAS the parties have established a long standing co-operation regarding the development, manufacture and sale of highly purified, high molecular weight, sterile hyaluronate, used in the field of pharmaceuticals (human or veterinary). This co-
operation does not, however, include hyaluronic acid, cross-linked to itself or to other substances, but

WHEREAS the parties now have become interested in the development of modified (cross-linked) hyaluronic acids as well, and wish to co-operate in the exploitation of ideas within this area, and

WHEREAS Balazs, as the world’s leading expert in the area, wishes to devote his full capacity to the development of hyaluronic acid as aforesaid and has a number of ideas in connection herewith, and

WHEREAS Pharmacia has a world leading position in cross-linking technology and separation technology as well as in the manufacture of hyaluronic acid....”

The negotiations that took place on September 23 were followed by a more specific proposal regarding the undertaking, signed by Erik Danielsson on October 6, 1981. The proposition also detailed how ownership of the new company would be divided, as well as Pharmacia’s financial contributions to its operation.

Despite a promising beginning, the plan fell through the cracks and was not pursued further. Still wishing to put the ideas into action, Balazs pushed on under the supervision of the newly created Biomatrix. Cooperation with respect to ocular treatment between Pharmacia and Biomatrix would, however, continue. Already by December 1 of the same year, a memorandum of understanding had been brought forth by the two parties, stating the following purpose of action:

“NOW THEREFORE it is proposed that the parties enter into an agreement under which Biomatrix will undertake on behalf of Pharmacia certain research and development projects relating to the ophthalmic applications of cross-linked hyaluronic acid, in return for which Biomatrix shall receive certain payments and royalties from Pharmacia.”

Discussions regarding a future collaboration even beyond ocular medicine are still present despite the previous plans having ground to a halt. This was made evident by Erik Danielsson’s May 19, 1982 letter in which, after first sending congratulations to Balazs’ wife Janet for having successfully defended her PhD thesis, Danielsson goes on to mention the previous discussions about a future partnership developing joint supplements:

“Let me stress once again that I can hardly see any project within the Division that should be given higher priority than the human joint project.”

Despite Danielsson’s assurance, no collaboration within the field of joint supplements materializes. This came as no surprise to Biomatrix, as they were aware of Pharmacia’s
lack of interest in osteoarthritis, or in any case that there was a faction within Pharmacia that was working against development of hyaluronic acid for osteoarthritis. Janet Denlinger made no secret of this in an interview for the book “More Conversations with Hyaluronan Scientists” (2011).

When asked: ”When did you stop doing basic research?” she replied: “When I finished my PhD in 1982 and we came back to the US, we decided to leave Columbia and devote our full attention to Biomatrix. We had to do that because we realized that Pharmacia, the Swedish company that had the license for Bandi’s Healon, was not going to be able to do everything that we wanted to do with Healon or hyaluronan in general: mainly, to put it into joints and solve the problem of arthritis.”

Presumably, it was Pharmacia’s respect for Balazs’ expertise that made them opt to continue discussions regarding the use of hyaluronic acid for joint treatment. Despite doubts regarding a breakthrough for such use of the molecule, there was too much at stake if Balazs were to succeed and a competitor was rewarded by his efforts.

Pharmacia would ultimately play a central role in the financial progress of Biomatrix, despite its reluctance to invest in the use of hyaluronic acid for joint treatment. In the meantime, Biomatrix would need to rely on revenues from skin care products, contributions from its owners and venture capital.

New types of hyaluronic acid are discovered

In 1983, research and development at Biomatrix was successful in discovering and producing new derivatives of hyaluronic acid. Through a process of crosslinking a so-called hydrogenated gel was formed. It was given the generic name hylan B. Originally produced in order to replace the vitreous humor during surgery for retinal detachment, hylan B was later one of the main ingredients in Hylaform®, a skin care product launched by Biomatrix. The product was introduced to the cosmetics market in the 1990’s as a wrinkle reducer. In 1984, Biomatrix released news of the development of hylan A, a derivative of hyaluronic acid with a very high molecular weight. A year later, success was achieved in combining hylan A and hylan B. The result was a sterile, viscoelastic liquid, free from pyrogens. Hylan G-F 20, as it was called, would prove invaluable as the main ingredient in Biomatrix’ most important product, launched during the mid-1990’s under the brand name Synvisc.

15 “Bandi” is Endre Balazs nickname among family and friends
Renewed, and now fruitful negotiations with Pharmacia

A mere three years after its introduction on the U.S. market, Healon had become Pharmacia’s single highest-selling product, with sales of 43 mUS$. By the end of 1984, with sales pushing 63mUS$, Healon was responsible for a fifth of Pharmacia’s total sales, and even more of the company’s total profit. As licensor, Balazs’ company Biotrics was awarded approximately 2.65 mUS$ during 1984. Also notable during 1984 was Erik Danielsson’s taking over as CEO for Pharmacia AB after Gunnar Wessman.

During 1985, likely as the result of increased mutual benefit with regard to the success of Healon, there was a breakthrough in negotiations between Biomatrix and Pharmacia regarding closer collaboration. The parties united in agreeing to a five-year research and development contract focused solely on ophthalmology. In addition, Pharmacia agreed to buy 80,000 stocks in Biomatrix, worth 1.15 mUS$, through its American subsidiary, Pharmacia Development Company, Inc. Two years later, yet another acquisition took place, resulting in Pharmacia again buying stock in Biomatrix, this time totaling 3.04 mUS$. At this point, Pharmacia’s ownership of Biomatrix had increased to 8.1%. Also of importance for Biomatrix, the acquisitions were preceded by Channing-Weinberg Venture Capital becoming the single largest independent owner of Biomatrix a year earlier.

The research and development contract between Pharmacia and Biomatrix was considered one of the year’s most significant events, as described in Pharmacia’s annual report from 1985. What the contract entailed in terms of compensation for Biomatrix was some 500,000 US$ from 1986 to 1990. The contract was followed by other agreements between the parties. During the latter half of the 1980’s, Biomatrix was awarded a contract to perform quality control for Pharmacia, administering the so-called owl-monkey eye test on Healon for Pharmacia Ophthalmics. In addition, Pharmacia Ophthalmics was awarded a distribution agreement for hylan fluid (hylan A) and hylan gel (hylan B). Subsequently, Biomatrix received an advance payment of 3 mUS$ in 1987 for future royalties. The agreement was extended in 1992 with regard to hylan fluid, resulting in an additional advance on royalties of 3 mUS$ for 1993-1995. Pharmacia also agreed to pay minimum annual royalties of 1 mUS$ during a seven-year period beginning in 1996.

The agreements with Pharmacia now yielded the bulk of Biomatrix income from the mid-1980’s into the 1990’s. Despite this, Pharmacia’s role as licensee and part owner of Biomatrix proved to be a source of increasing frustration for Endre Balazs. Balazs’ growing dissatisfaction was made evident during an exchange of letters between himself and Erik Danielsson from October 1987 until November 1989. In spite of this, Balazs still held optimism regarding future collaboration. In a letter dated October 14,
1987, just as negotiations regarding a second stock acquisition by Pharmacia were about to be completed, Balazs writes:

"Just about 15 years ago, Pharmacia and I started to negotiate an association which proved to be very profitable indeed for both of us and, even more importantly, created a new type of treatment in medicine. In addition to this success, the past 15 years also fostered a chronic frustration for me. That is, the failure to convince Pharmacia that the new technology offered by the use of viscoelastic substances in medicine presents a great opportunity for the treatment of musculoskeletal disorders in man. About a month ago I was ready to give up all hope that our complete cooperation in this field could be achieved. Then suddenly you created a new opportunity, and my optimism was once more challenged. Now it seems that we are ready to make the first step toward the integration of the two companies’ efforts to market a new family of products for medicine and to repeat our previous success on a scale ten times greater."

The letter is closed by an appeal from Balazs:

"You and I have been in agreement for a long time that a full cooperation between our companies is essential for the success of our pioneering effort in medicine. Please, do not let this opportunity pass. The timing of our filing for the public offering, as insisted upon by our underwriter, requires that this first step toward our ultimate cooperation be executed before the end of this week."

On Monday, October 19, 1987, Pharmacia and Biomatrix reached an agreement that involved a much-needed capital boost for Biomatrix in the order of 3 mUS$. Confirmation of the deal came as Biomatrix’ board of directors sat in their board meeting at the prestigious University Club in New York regarding a possible listing on Nasdaq. Some hours later, the world economy would experience the second largest stock market crash of all time, known as “Black Monday”. Biomatrix’ newly appointed President and Chief Operating Officer, George Oram, remembers vividly as financial analysts involved in discussions came and went out of the room. When word of the market crash came, continued discussions were postponed indefinitely. They would not resume for some three years. In hindsight, the timing with which Pharmacia increased stock ownership in Biomatrix proved to be monumental.

Portions of Endre Balazs’ response to Erik Danielsson on October 20, 1987 read:

"Dear Erik, I am very pleased that we signed yesterday the second agreement between Pharmacia and Biomatrix. I am confident that this heralds a most fruitful cooperation between our companies, not only in ophthalmology, but also in the field of musculoskeletal diseases. ... In order to ‘proceed expeditiously and in good faith’ in starting the activities outlined in the recently signed ‘Letter of intent’, I would hereby like to let
you know the names of the representatives of Biomatrix for the Steering Committee: Endre Balazs, Janet L. Denlinger, George Oram, Bengt Ågerup, André Balazs.”

One can assume that there were those at Pharmacia who raised their eyebrows when they learned about Biomatrix’ formation for the Steering Committee: Bengt Ågerup, the dismissed CSO of Pharmacia Ophthalmics, back in business, but on the opposite side of the table in his role as newly appointed CEO of Biomatrix’ Swedish subsidiary.

**Pharmacia balks at additional investment in Biomatrix**

The hope instilled after Pharmacia’s second stock acquisition in Biomatrix during October 1987 is not actualized. A letter from Endre Balazs to Erik Danielsson written February 26, 1988 contained the following:

"Dear Erik, Thank you for your letter of February 22, 1988. Unfortunately, the discussions between Pharmacia and Biomatrix slowed down after our last meeting in mid-February, which at that time appeared to be successful….. This is very unfortunate, because in 1987 a Japanese company\(^\text{16}\) sold 25 million dollars’ worth of hyaluronic acid for osteoarthritic patients on the Japanese market based on the same medical indication that was part of the worldwide license agreement with Pharmacia in 1976.

...While in 1980 it was only Pharmacia that sold hyaluronic acid, today at least a half-dozen companies are active in various market areas. Pharmacia has already lost its leadership position and I see very little chance that it can recapture it. ... I am determined to retain Biomatrix’ leadership in the field, and capture directly or indirectly a large part of this market. If Pharmacia wants to participate, it has to be according to our plans.

It is unfortunate that Elof Johansson\(^\text{17}\) cancelled his participation at our last board meeting. As you know, at your suggestion we invited him to that meeting, and he first planned to attend but later cancelled.”

Worth noting was the fact that Endre Balazs had presented a proposal regarding a possible third acquisition at the onset of 1988. The plan would have made Pharmacia one of Biomatrix’ largest owners. However, the proposal never materialized.

\(^{16}\) Seikagaku, which company in 1987 launched the product ARTZ, which later has been sold in Sweden through Astra-Zeneca under the brand Artzal

\(^{17}\) Elof Johansson was during 1984-90 director of research at Pharmacia AB, and vice president and executive board member 1986-90
Elof Johansson explains his absence from the Biomatrix board meeting in a letter dated March 8, 1988. He makes reference to earlier agreements with regard to research collaboration between Pharmacia and Biomatrix. He then moves on to write:

"From our recent contacts we have, however, understood that Biomatrix is first of all interested in a long term financial solution leading to a dominating investment by Pharmacia."

Given the fact that Pharmacia had assigned Pharmacia Ophthalmics all responsibility for hyaluronic acid, Johansson goes on to explain why an ownership increase: "...would not be a clear one and resources would be more overlapping than complementary." Given this, Johansson’s stance is made clear: "We are for this reason not prepared to increase our investment in Biomatrix beyond the present level."

Elof Johansson’s letter is followed by that of Erik Danielsson, dated March 25, 1988:

"Dear Bandi:

By now you should have received Elof Johansson’s letter explaining the fact that Pharmacia is not prepared to make a further investment in Biomatrix.

I would like to take this opportunity to expand on the matter on a more private basis. Although I am of course fully behind the decision, I cannot help thinking that it is a pity that this had to be the conclusion, as there is still no doubt that we in almost all respects belong together… The amount of money discussed is huge indeed and our people insist that there is alternative use of these resources that would be considerably more profitable for us as we have already to quite some degree the same competence as Biomatrix."

The letter concludes:

“Even if we are not going on with the investment, our companies are in many respects interlinked and we should try to keep the door open if anything happens that would make a renewed discussion of interest for both parties.”

During the exchange between Balazs and Danielsson, Pharmacia Ophthalmics presents its sales statistics for 1987. The results showed continued success, as sales increased from 105 mUS$ to 160 mUS$, of which Healon accounted for approximately 85 per cent. Balazs should have been rewarded accordingly by Pharmacia’s success. According to the 1976 agreement between Pharmacia and Biotics, Balazs was to be paid 4.2%, which would correspond to a royalty of approx. 3.7 mUS$ for 1986 and 5.7 mUS$ for 1987. However, Balazs was unaware that Pharmacia was about to cease to pay royalties from markets where Healon had been sold for more than ten years. According to Pharmacia’s interpretation of the license agreement, they were not
obliged to pay royalties after ten years, starting from the date of the first commercial sale and regardless of the medical application for which Healon was sold. Pharmacia’s maneuver had its largest impact in terms of the French market, where Healon had been sold since 1976 under the name Healonid Vet. Needless to say, Balazs did not share Pharmacia’s perception of the agreement when he became aware of it a couple of years later.

Pharmacia and Balazs – an unraveling partnership?

Balazs is first congratulated in Erik Danielsson’s September 1, 1988 letter for Biomatrix having received “IDE approval”\textsuperscript{18} from the Food and Drug Administration (FDA) for hylan: ”... This must be an important milestone for Biomatrix’ scientific achievements.” Danielsson then goes on to mention that R&D chief Gösta Jonsson will replace Elof Johansson as Pharmacia’s representative on the Biomatrix board. Then to the more important purpose of his letter; namely, two questions deemed: ”... very important for the cooperation and relations between Biomatrix and Pharmacia.”

Danielsson’s first concern is how the definition of the term “product” should be handled in regard to the 1976 license agreement for hylan. He suggests that experts from Biomatrix and Pharmacia meet in order to sort out the details once and for all\textsuperscript{19}.

The second question touches on Biomatrix marketing of its product Synvisc Vet in Europe. Worry had arisen within Pharmacia when those in charge of sales contacted Bengt Ågerup about what they believed to be mistakes by Biomatrix in analyzing a clinical trial. Despite assurances by Biomatrix, no corrections of the analysis had been done. In addition, despite the fact that the product was only registered in The Netherlands, it had become available in West Germany and Scandinavia. Danielsson ends his letter: ”I would be most grateful if you could investigate this situation and ensure that the European Biomatrix operation does not put unnecessary friction into our important relations.”\textsuperscript{20}

\textsuperscript{18} IDE stands for Investigational Device Exemption and means that a device can be used in a clinical trial to collect necessary data about security and efficiency for a Premarket Approval (PMA) or a Premarket Notification (510-k) to the Food and Drug Administration (FDA).

\textsuperscript{19} Suggesting that hylan should be included in the original license agreement actually means that the entire “raison d’etre” of Biomatrix is challenged.

\textsuperscript{20} Bengt Ågerup has during 1987 started the first clinical trials of hylan G-F 20 on horses in Sweden. The product will later be sold under the trademark GelViscVet. The same year clinical trials for the same product on human osteoarthritis are started in Holland. This product will be sold under the trademark Synvisc.
Balazs responds to Danielsson’s letter two weeks later. As to Danielsson’s proposal about a meeting to discuss the 1976 license agreement, Balazs makes clear that the matter has nothing to do with Biomatrix, but rather with him personally, and therefore it does not make sense for company representatives to meet. He does, however, express urgent interest in discussing the matter directly: ”I am very disturbed by the inactivity of the Healon Board and by the increasing hyaluronan sales by European and Japanese companies for the treatment of arthritis.”

Regarding the reference to Synvisc Vet. having been distributed beyond The Netherlands, Balazs refers the matter back to Bengt Ågerup and reminds Danielsson of the same occurrence having been experienced in the case of Hylartil® Vet’s release in Australia by Pharmacia. In short, not much could be done about the problem.

On February 14, 1989, Danielsson congratulates Balazs on Biomatrix’ recently successful equity issuance. ”The fact that you and Jenti [Janet Denlinger] are part of it is an excellent expression of your faith in the future of Biomatrix.” The issuance had given Biomatrix additional financial assets in the order of 5 mUS$.

Toward the end of July 1989, a private letter from Endre Balazs, dated July 19, was placed on Erik Danielson’s desk. The sole basis of the letter was to discuss Balazs’ growing concerns with the 1976 license agreement. Though private in nature, the letter would have significant consequences even with regard to the business relationship between Pharmacia and Biomatrix Inc.

The letter consisted of two parts, the first of which presented five specific points, for which Balazs wished for an immediate response. The second part of the letter touched upon a larger though nonetheless specific problem that concerned Balazs; namely Pharmacia’s inactivity regarding a launch of Healon on the human osteoarthritis market. Balazs continued to argue that Healon’s largest potential market continued to go unnoticed.

The initial four points address the following:

- A request for documentation showing that Pharmacia was following the clause of the license agreement regarding the maintenance of the patent and brand protection for Healon
- A request for documentation showing that NIF-NaHA was only being utilized for those products for which Pharmacia was paying royalties
- A response as to why activity of the Healon Board had ceased
- A request for information regarding improvements in manufacturing, packaging and testing for Healon since 1976
The fifth and final point made clear that Balazs did not believe Pharmacia had fulfilled its obligation with regard to developing Healon according to “best efforts”, as stipulated in the license agreement. Highlighting this opinion was the fact that there were two companies selling hyaluronic acid-based products for human arthritis since 1987. Sales by the two companies, based in Japan and Italy, exceeded an estimated 100 mUS$.

On this, Balazs writes:

"The fact that these two companies embraced and acted upon my scientific and medical concepts and inventions to treat human arthritis with NIF-NaHA, while at the same time my partner in technology and business, Pharmacia, neglected its contractual commitments, is a major profession embarrassment for me. In addition, this also, of course, represents a very substantial economic loss to me personally. Therefore, I request financial compensation for this loss and the immediate return to me of rights to Healon (NIF-NaHA) for my exclusive use in the field of human arthritis worldwide."

In conclusion: “I have brought these matters to your personal attention, and to your attention only, at this time with the expectation that they will promptly be addressed. I will appreciate hearing from you very soon about this. Together, I hope that we can work to our mutual benefit to address these issues. This is the course I would prefer to follow at this time; however, if we cannot work this out together soon I shall be forced to explore all of my other options.”

Balazs would wait more than a month for Danielsson’s reply, dated August 24, 1989. Danielsson reminds Balazs that he had already in September 1987 raised the question concerning the relationship between hylan A and B and the original license agreement. Furthermore, Danielsson suggests that experts from both companies meet in October for more discussions regarding “matters considered unsettled.” Out of regard for the imminent and rapidly approaching hearing scheduled for September 24-26, Danielsson suggests that such an expert meeting be held in October.

Balazs is not satisfied by Danielsson’s reply. This is clearly understood in a subsequent letter dated September 6, 1989. Balazs writes:

"Although I appreciate your letter of August 24, 1989, I would like to point out that I originally wrote to you on July 19 to obtain specific answers to questions that have arisen with regard to my 1976 License Agreement with Pharmacia. I directed my letter to you – instead of sending it as a formal notification as provided for in the Agreement – partly because the Agreement was signed by the CEO at that time but, principally,  

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21 The hearing Danielsson refers to concerns Pharmacia’s lawsuit against Med-Chem for patent infringement.
out of respect for our long-standing friendship. I stand firm, however, in my insistence
upon answers to the questions raised in my letter. I will need these answers, not a
meeting, in order to assure our continued cooperation in our remaining fields of mutual
respect.”

The questioning of hylan A and B’s correlation to the 1976 license agreement is
regarded as nonsense by Balazs. His claim is that the technology on which the hylans
are based is completely unique:

"Hylans are new chemical entities invented by me and my colleagues. In the expert
opinion of the inventors of hylans and the examiners of patent offices from various
countries of the world, these new polysaccharides are derived from natural hyaluronan
by crosslinking processes. As clearly defined in the 1976 agreement, not included is:
‘… hyaluronic acid crosslinked to itself or to other substances.”

Furthermore, Balazs notes that Pharmacia has been well aware of his work with hylans
for more than eight years. At one point, he even invited Pharmacia to engage in a
cooperative venture regarding hylans, of which he reminds Danielsson: ”... remember
our discussions in Villefranche and Cannes summer 1981.” Balazs’ proposal was
dismissed by Pharmacia, prompting the birth of Biomatrix. Despite being one of
Biomatrix’ largest owners, Pharmacia has continually declined to partake in proposed
joint endeavors with regard to further commercialization of hylans. The only area of
application of interest for Pharmacia continued to be that of ophthalmology. This does
not surprise Balazs given:

"Pharmacia has not exploited the medical use of my previous invention, NIF-NaHA,
in any field other than ophthalmic viscosurgery and veterinary medicine during the 17
years it has had exclusive rights to do so.”

Balazs’ letter ends: “In conclusion, I want the answers to the questions in my letter of
July 19 now, not in October. With the answers in hand I will be ready to discuss with
you where we are now and where we are going in our cooperation in fields of mutual
interest. With best personal regards, Bandi.”

Balazs would have to wait until early November until he received a detailed
explanation with regard to the questions posed in his letter of September 6. To
Danielsson’s defense, he did indeed write to Balazs already on October 6 in order to
inform him that an in depth response would be delayed. When Danielsson’s reply is at
last written, the five points brought up by Balazs are all addressed at length. Danielsson
also adamantly defends Pharmacia against the claim that the company had not put forth
its “best effort” in working toward advancements on the human arthritis market. Also
contested are claims by Balazs that the hylans were not to have been subject to the
1976 license agreement.
Danielsson then went on to satisfy Balazs’ request for information on what exactly had been done with respect to maintenance of patent and brand protection for Healon. Here, Danielsson admits to one instance in which Pharmacia has sold NIF-NaHA based products for which no royalties have been paid. The product in question, Sperm Select®, had been sold in small quantities for research purposes according to Danielsson. Funds received in conjunction with the sales of Sperm Select would be accounted for in the upcoming royalty statement. The fact that the Healon Board no longer met was not able to be resolved. As Danielsson explained, the Board was brought to life during a time before the existence of Biomatrix. The initial open nature of the Healon Board was hampered by the overlapping nature of the two companies’ operations and the ensuing impact regarding secrecy requirements.

With respect for developmental work on the human arthritis market, Danielsson referred to a number of steps that had been taken to this accord by Pharmacia. In summary:

“Having all of this in mind I do honestly believe that Pharmacia is indeed pursuing the human arthritis and other uses of NIF-NaHA. Pharmacia is definitely not in default of its obligations under the 1976 Agreement. Pharmacia can therefore not accept your request for financial compensation and return of rights to Healon (NIF-NaHA) for your exclusive use in the field of human arthritis worldwide.”

On “the hylans,” Danielsson insists that there exists “… an honest difference of opinion.” He writes:

”You claim that hylan is a new chemical entity, as evidenced by the inventors and the examiners of patent offices from various countries. We have, of course, also had outside legal experts analyzing this thoroughly who have concluded that hylan clearly falls within the 1976 Agreement. So far, we have refrained from pursuing this argument as I have always believed and do still believe that we shall solve our differences in a business rather than legal manner.”

Danielsson concludes: “Bandi, just as your relationship to Pharmacia is important to you, so is Pharmacia’s relationship to you and Biomatrix. Over the years this relationship has been built on trust and mutual benefit. Relying on this relationship we have a good basis for settling our differences and to come to a mutually beneficial arrangement.”

Danielsson’s letter of November 2, 1989 marks the end of a 15-year long collaboration between him and Endre Balazs. In April 1990 Pharmacia is merged with the Swedish pharmaceutical company Kabi, and Kabi’s CEO Jan Ekberg is named CEO for the new company. After a short stint as deputy CEO of Procordia, the owner of Kabi Pharmacia, Erik Danielsson resigns, as does Jan-Erik Engkvist, the CEO of Pharmacia.
Ophthalmics. As a result, no one at the helm of Kabi Pharmacia has any advanced knowledge of Healon’s history nor any deeper relationship with Endre Balazs himself. The only remaining character from the time of the 1976 license agreement is Carl Engholm, in charge of the patent and brand division. Further weakening Healon’s standing was the merger itself, which resulted in relinquishing its place as top product. This position was now awarded to Genotropin. Toni Weitzberg, previously marketing director and deputy CEO, and employed at Pharmacia since 1983, becomes the new CEO of Pharmacia Ophthalmics.
CHAPTER 14: Biomatrix’ Swedish subsidiary

As Bengt Ågerup was being forced from Pharmacia at the end of 1984, he had already agreed to begin work at Biomatrix as a consultant. Made evident by a fax sent from Balazs to Ågerup on October 3, 1984, Ågerup is promised a minimum of 33 days consulting work during the coming year. In exchange, Ågerup is to be paid 300 US$ per day. Balazs is anxious to meet Ågerup and writes from Alicante, where he is currently staying:

"It is expected that during November 1984, you will visit Biomatrix, Inc. and discuss further details of extending this agreement or transforming it to an employment agreement. During this visit, your future role and responsibilities at Biomatrix, Inc. will also be discussed."

A formal contract regarding Ågerup’s consultancy is signed on December 14, 1984 between Ågerup and Endre Balazs’ son André, who has been appointed Executive Vice President for Biomatrix. The agreement amends the earlier agreed upon amount of work to be performed by Ågerup and states: “a minimum of 36 days and a maximum of 120 days annually.” The originally discussed payment of 300 US$ per day is confirmed and the agreement spans three years.

Also included was a clause deemed: “Agreement Not to Compete”, where the following was made clear:

“… the Consultant shall not, within any foreign or domestic jurisdiction in which the Company conducts its business, engage in or own an interest in any entity which engages in activities in competition with aspects of the Company’s business concerning which the Consultant has performed services hereunder, including but not limited to the invention, development, testing, use and manufacture of hyaluronic acid, collagen, elastin, and natural or synthetic polymers or bio-materials as applied to or for use as skin care, medical or surgical products or processes. These restrictions shall continue for a period of three (3) years after termination of the Agreement.”

The agreement results in significant contributions by Ågerup in terms of initiating clinical trials in Europe for hylan G-F 20, a combination of hylan A and hylan B for the treatment of arthritic pain in humans and animals. As Ågerup’s work continues, discussions surrounding the legal framework of the consultancy agreement develop. In a letter from Balazs to Ågerup dated May 30, 1986, Bengt Ågerup is offered 73,778 shares of Biomatrix stock in light of “… his newly expanded role in Biomatrix.”

In August of 1986, Bengt Ågerup is formally employed by Biomatrix. Though his workload would vary from full time to part time, he would remain with the company
until 1997. In 1987 he is appointed CEO of Biomatrix’ Swedish subsidiary, Biomatrix Svenska AB, a position he keeps until he leaves the company in 1997.

**Up-Will Investor KB - redemption for Biomatrix**

Among the essential factors in the success seen by Biomatrix was a fund raising project organized at the beginning of 1990 through the company Up-Will Investors AB. The purpose of this project, which was initiated by Bengt Ågerup, was to secure the financing of ongoing clinical trials for Synvisc in Europe.

The creation of Up-Will Investors was related to the development of Biomatrix as a whole. As earlier mentioned, Biomatrix’ most significant source of income during the 1980’s could be attributed to joint research projects with Pharmacia Ophthalmics. In addition, Pharmacia AB had also purchased stock in Biomatrix, further boosting capital. Despite this, serious plans surrounding yet a third stock acquisition in 1988 by Pharmacia AB never materialize. A third such acquisition would have made Pharmacia AB the single largest owner of Biomatrix. As a result, Biomatrix decided at the beginning of 1989 to greatly reduce funding to its Swedish subsidiary, from 50,000 US$ monthly to a mere 19,000 US$.

The decision to significantly reduce funding threatened to force clinical trials of Biomatrix’ principal products, Synvisc and Hylaform, in Europe to a grinding halt. It was at this point Ågerup began toying with the idea of alternative funding from Up-Will Investor AB, a company he owned together with Bernt Vikström. In addition to Up-Will Investor AB, the duo also owned Equinord KB, holder of European distribution rights for GelViscVet, the veterinary version of Synvisc.

In Biomatrix Svenska AB’s management discussion and analysis portion of the annual report for 1990, Bengt Ågerup gives the following account:

“Three people were employed during the year, one of which on a part time basis. Nearly two mSEK have been spent, mostly in conjunction with different projects. Profits have been modest.

The parent company’s long road toward self-sufficiency has once again taken a toll on its Swedish subsidiary. As a result, the subsidiary requires more and more freedom except in those cases that services are performed directly at the request of the parent company. Instead of relying on funding from the parent company, an external group of investors has been obtained in order to further the company’s most critical focus – osteoarthritis. The group has promised funding in the order of 9 mSEK (≈ 1.5 mUS$) in exchange for future royalties. In more direct terms, royalties would be distributed as a result of the group directly funding clinical trials in Europe. Furthermore, additional
funding has been promised by yet another group of investors, Equinord KB, for establishing the veterinary use of Biomatrix’ products in Europe. Equinord KB possesses exclusive distribution rights from Biomatrix. As a result of lacking funds and the unavailability of certain key individuals, all other activities by the Swedish subsidiary will be halted indefinitely.”

What Ågerup refers to as “…another group of investors, Equinord KB”, is, as mentioned above, a company owned by Ågerup himself together with his friend Bernt Vikström. Vikström will leave Equinord KB in 1996, leaving sole ownership in the hands of Ågerup.

The injection of capital through Up-Will Investor AB is to be administered through a so-called limited liability partnership. The new company is called Up-Will Investor KB. Business colleagues, friends and relatives are invited to make financial contributions to the newly formed company in exchange for partial ownership. The contributions ranged from 500,000 to 1,000,000 SEK. The move resulted in raising 7 mSEK (≈ 1.2 mUS$). Ågerup and Vikström gained ownership relating to contributions of 1 mSEK (≈ 0.17 mUS$) each in exchange for future labor, so-called sweat equity. Other private contributors included Endre Balazs and Teresita Bennet. Ms. Bennet had been an assistant to Balazs at the Retina Foundation in Boston many years prior. At this time she was living in Switzerland, assisting Bengt Ågerup with a syringe filling device that Biomatrix had installed in Geneva in order to meet the constant need for syringes during clinical trials. Also part of the group of investors were two of Ågerup’s future partners at Bohus BioTech AB; the former CEO for Pharmacia Ophthalmics Hans Åkerblom and Bengt’s cousin, Göran Ågerup. Bohus BioTech AB is a company that will be returned to below and in Part V.

The new partial owners of Up-Will Investor KB were assured royalties from Biomatrix in the order of 6 percent during the following 10 years for all sales of Synvisc in Germany, France, Spain and the United Kingdom. It would be a profitable investment. Accounts differ as to exactly how profitable the venture was, but reasonable speculation leads one to believe that the investors were rewarded six to eight times their initial investments.

The first annual meeting of Up-Will Investor KB: I was there!

When reviewing my notes from the early 1990’s I came to remember that I was actually present at the first annual meeting for Up-Will Investor KB. The meeting took place at Hotel Reisen in Stockholm on February 8, 1991. As part of updating my business case on Healon, I was invited to the meeting by Bengt Ågerup after having interviewed him a couple of weeks earlier. Aside from mere interest in the meeting itself, Ågerup
thought that it would be a good opportunity for me to meet Endre Balazs and Janet Denlinger. Though my conversation with Balazs and Denlinger at the hotel that day was short, it further sparked my interest in Healon and the individuals involved.

**Ågerup with time on his hands**

Decreased financial support to Biomatrix Svenska AB during 1989 meant that the company could no longer afford to employ Bengt Ågerup as CEO on a full time basis. Ågerup’s sudden abundance of free time would have significant consequences. He wasted no time in investing more of his efforts into his own company, Q-Med AB. He also intensified the planning activities he had already started together with one of his former associates at Pharmacia Ophthalmics, Daniel Ogbonnaya, aiming at, among other things, developing products intended to compete with Healon on the eye surgery market. Ogbonnaya was at this time still employed at Pharmacia Ophthalmics. Their plans were finally realized in 1992 when they started Bohus BioTech AB, producing hyaluronic acid for the ophthalmology market. Ågerup’s role in Q-Med AB and Bohus BioTech AB are examined more in detail in Part V.

Investments from Up-Will Investor KB as well as improved financial standing for the parent company enable Bengt Ågerup to again work full time as CEO for Biomatrix Svenska AB. The change was initiated after a memo from Endre Balazs on December 9, 1991:

“"This is to confirm that the enclosed budget submitted by you on December 4, 1991 is accepted. Accordingly for October, November and December 1991, we will transfer US$10,000 monthly which will cover expenses, including 25% of your salary and other salaries and expenditures carried out by Biomatrix Sv. From January 1, 1992 until June 30, 1992, we will transfer US$15,000 monthly. The extra US$5,000 will be to cover expenditures including salaries related to the “senior trialist” which I understand will be a person with experience to supervise and monitor clinical trials. It is expected that from July 1 to the end of the year the monthly allocation will be US$20,000. At that time the activities under the Synvisc Project supported by Up-Will will be decreased and Biomatrix Inc. supported projects will increase.

It is understood that your yearly, full-time salary is US$108,000 starting October 1, 1991. Twenty-five percent of this will be paid from Biomatrix funds and 75% from Up-Will funds.”

Ågerup’s own views with regard to his work at Biomatrix during the same period are accounted for in a letter addressed to Endre Balazs and Rory Riggs (President of Biomatrix 1996-2000) of May 24, 1997.
“...In 1990 (March) the Up-Will was contracted and the funding was secured. This whole solution was possible because I promised to take care of the operation and finish the studies. So Biomatrix was activated and new people were employed. I myself saw an engagement taking about 50% of my time. This later was increased to be a full time engagement. Among other things we also started to think about and make investigations regarding new applications of the hylan technology.

Well, Synvisc was approved in Sweden and more and more of the work was moved to other arms of the organization – so by 1994 there was less and less for us to do. In the first half of 1995 the staff was reduced to what was needed to finish up all operations and first of July 1995 we had no one on our pay-roll. I was to continue to act as president and was going to be paid from time to time. I was then engaged by training the sales force of Roche, supporting John22 in negotiations with distributors, but finally the activities fell to a zero level..... In the end of March 1997 N.N. took over as president.”

While working from half to full time as CEO of Biomatrix Svenska AB, Bengt Ågerup also had a number of other relevant business ventures going on during 1992-1994. One such venture was his work as CSO at the newly formed Bohus BioTech AB, where he was also initially 50% owner. Simultaneously, Ågerup worked as a consultant for intraocular lens maker Corneal in order to train them to produce their own rooster comb-based hyaluronic acid. His contributions at Corneal lasted from late 1992 until 1994. As part of yet another project, Ågerup continued to oversee research and development at Q-Med, the company he started at the beginning of 1985, shortly after leaving Pharmacia. He would be awarded for the fruits of his labor at Q-Med when the patent application for the NASHA technology is filed in 1995 and Restylane is released onto the market in 1996. More about this can be read in Part V.


At the outset of the 1990’s, Biomatrix was still a small company focused on research and development. It had approximately 15 employees and very limited earnings. Its operational costs were covered in large part by a series of development ventures with Kabi Pharmacia Ophthalmic Division (the new name of Pharmacia Ophthalmics) and by new equity issuances. The issuance in 1989 worth 5 mUS$ was followed by yet another in 1991 that gave Biomatrix in excess of 26 mUS$.

Renegotiation of the 1976 License Agreement

By the beginning of the 1990’s, a tight web of interdependency had been woven between Endre Balazs, Biomatrix and Kabi Pharmacia Ophthalmic Division. Healon was Kabi Pharmacia’s second largest product, and sales continued to increase despite more competition and falling prices. The patent for Healon was set to run its course in 1996, which forced Kabi Pharmacia to maintain good standing with license holder Endre Balazs. Though Balazs was extremely unsatisfied with Kabi Pharmacia’s handling of Healon for the human arthritis market, sales of Healon on the eye surgery market were yielding royalties to him in the order of 6-7 mUS$ per year. Biomatrix saw large yields as well. Through the different cooperation agreements with the Ophthalmic Division regarding hylan fluid and hylan gel, Biomatrix received over 1 mUS$ per year in the form of research and development grants and minimum royalties. Not to be forgotten either is that Kabi Pharmacia was one of Biomatrix’ largest owners.

Though this weave of cooperation had benefitted all involved, it would prove to be as distressing as profitable. Several members of Pharmacia’s Ophthalmics Division felt apprehensive about Bengt Ågerup’s presence in his role as CEO for Biomatrix’ subsidiary in Uppsala. Concerns within the division’s management team increased when it became known that Ågerup was involved in starting a new company, Bohus BioTech AB, with former Pharmacia contributor Daniel Ogbonnaya, among others. The purpose of this new company was to produce rooster comb-based hyaluronic acid. In other words, Bengt Ågerup was involved in the creation of a direct competitor to Kabi Pharmacia. Additionally, his actions would help create an indirect competitor to Endre Balazs in his role as licensor for Healon. Neither Endre Balazs nor Biomatrix were informed of the scheme.

Meanwhile, steady criticism from Balazs regarding Kabi Pharmacia’s lack of intent on the human arthritis market was still present. Balazs also continued to demand economic
compensation as a result, in addition to changes in the license agreement. These uncomfortable points of conflict put Kabi Pharmacia in a difficult position. The situation is described by Toni Weitzberg, new CEO for the Ophthalmics Division after J-E Engkvist’s departure, as if “Balazs held a sword over our heads.” In an attempt to diffuse tension, Weitzberg contacted Balazs and set up a meeting at the end of the summer in 1992. The purpose of the meeting was to re-negotiate the license agreement from 1976.

The negotiations took place at Balazs’ summer home outside of Saint Tropez on the French Riviera. Kabi Pharmacia was represented by Ophthalmics Division CEO, Toni Weitzberg, manager for the Patents and Brands division, Carl Engholm, and chief legal counsel Tomas Harryson.

The meetings resulted in an “amendment agreement,” signed by both parties on December 31, 1992. In addition, a “mutual release and covenant not to sue” was agreed upon and signed by the parties. As this portion of the agreement involved Biomatrix, CEO George Oram was involved, and signed as well. In short, the agreement established that all rights regarding manufacturing and selling Healon for eye treatments and veterinary purposes would be retained by Kabi Pharmacia. It was also agreed upon that Endre Balazs again received sole rights with regard to manufacturing and selling Healon for orthopedic purposes. The financial arrangement involved was relatively simple as it remained largely unchanged as compared to the original 1976 agreement. There were but two changes:

- Kabi Pharmacia agreed to pay Endre Balazs 2 mUS$ upon signing the amendment agreement.
- Kabi Pharmacia agreed to transfer its stock in Biomatrix Inc. (400,520 shares) to Endre Balazs without demanding financial compensation.

There are two important points of interest with regard to the amendment agreement:

- The product definition as explained in the original 1976 agreement was amended from merely: “hyaluronic acid cross-linked to itself or to other substances” to: “including without limitation hylans, as invented or developed by or on behalf of Endre Balazs, or Biomatrix, Inc.”
- Kabi Pharmacia shall cooperate fully and promptly with any audit that Endre Balazs or his representatives shall undertake in accordance with the 1976 Agreement.

The purpose of the more specific product definition was most certainly Balazs’ solution to the long discussion between himself and Erik Danielsson with respect to whether or not the hylans were part of the 1976 agreement. The second point of change
would be utilized by Balazs during the spring of 1993, as he arranged for an audit of royalties he had been paid from Pharmacia since the first option to license agreement in 1972.

In the end, the amendment cost Kabi Pharmacia approx. 6 million US$, a price they were willing to pay in order to have the sword removed from over their heads. Kabi Pharmacia now planned to utilize this newly purchased peace of mind in order to focus forward. Unfortunately, it was a false sense of security that came to an abrupt halt at the onset of Balazs’ planned audit over royalties, the details of which will come later in this chapter.

**Biomatrix’ dependency on Kabi Pharmacia lessens as revenues increase**

Biomatrix’ great dependency on Kabi Pharmacia is well documented in the publication “Biomatrix 1981-2000, a history of success.” A key event of 1992 is described: “Ten-year marketing agreement signed with Kabi Pharmacia Ophthalmics Division.” Among the key points described during 1993 was “Pharmacia invests 12.5 mUS$ in Biomatrix.” This refers to a distribution agreement regarding hylan fluid from October 1988, which was extended on December 31, 1992. Upon closer examination, part of the 12.5 mUS$ investment was in the form of anticipated future payments. The payments were to cover profits in accordance with Kabi Pharmacia’s exclusive distribution rights for hylan fluid (hylan A) on the human ophthalmic viscosurgery market. Further payments to the same end were made on January 1, 1993 for the period 1993-1995. The amount paid at that time was 3 mUS$. An additional 1 mUS$ per year for seven years, starting in 1996, was part of the deal. Clearly expressed in the agreement was Kabi Pharmacia’s right to terminate the agreement at any time upon 30 days’ notice at a cancellation cost of 1 mUS$.

The same period saw Biomatrix grow significantly. In order to increase efficiency, the company was divided into three new divisions. The new divisions were labeled Arthritis Division, Orlo Division, and Other Medical Products. Biomatrix’ production had grown to ten products, though only two would realize commercial success. Those two, Synvisc and Hylaform, are therefore to remain the focus of this chapter.

Biomatrix experienced two decisive events in 1995 that made further development of the company possible. Both Synvisc and Hylaform were awarded CE certification, opening the way for sales within the European Economic Community, consisting of 19 countries. The CE certification was a direct result of a project headed by Johann Scheidt, a Biomatrix employee of German origin. His main cooperation partners when working in Europe were Bengt Ågerup in his role as CEO of Biomatrix Svenska AB, and the head of the company’s European business office in Paris, started in 1992, John
Feilders. Scheidt became aware of the possibility of getting CE-marking 23 for Hylaform and Synvisc as medical devices in connection with a seminar in Weimar, Germany conducted by an expert on the EU Medical Devices Directive, Dr. Wolfgang Müller-Lierheim. With the help of the German expert, who represented a company that was accredited as a so-called Notified Body by the European Union, Biomatrix obtained the much coveted CE marks in November (Synvisc) and December 1995 (Hylaform).

During the summer of 2014, I talked to Johann Scheidt about his role in the process of EU certification for Synvisc and Hylaform. Though CE approval was received for both applications, it was not without some controversy in the case of Hylaform. The difficulty, according to Scheidt, was the direct result of Bengt Ågerup. Heavily involved in the project was a German plastic surgeon by the name of Dr. Johannes Reinmüller. During the process of the project, Scheidt discovered that Bengt Ågerup was working toward CE approval for Hylaform in his role as CEO for Biomatrix Svenska AB, but also for a competing product as owner of Q-Med AB. Dr. Reinmüller was heavily involved in both projects, likely the first plastic surgeon to test the world’s two first hyaluronic acid-based dermal fillers, first Hylaform and then Restylane. I decided to contact Dr. Reinmüller and we met in September 2014 in Wiesbaden, where he is still practicing plastic surgery. How it came about that he was involved in both companies more or less simultaneously will be returned upon in Part V.

Contrasting marketing strategies for Synvisc and Hylaform

Though both products showed early promise, Endre Balazs felt more optimistic, and cared more about Synvisc than Hylaform. Balazs was careful to consider his approach in terms of how to market Synvisc. Given his experiences in negotiating with Pharmacia and taking into account the heterogeneous nature of the arthritis market, he decided to divide sales and distribution rights among different companies. In contrast, it was decided that Hylaform would be best sold and distributed by a sole actor. The marketing strategy for Synvisc was developed by Endre Balazs in close co-operation with Rory Riggs, member of Biomatrix’ Board of Directors since 1990, and President of Biomatrix 1996-2000, and John Feilders, head of Biomatrix’ European business office in Paris since 1992.

Before starting the office in Paris, Feilders was involved in the establishment of Biomatrix’ subsidiary in Canada and in the purchase and start-up of the company’s production facility in Pointe-Claire, outside Montreal. Canada was the first country in

23 CE = Conformité Européenne
which Synvisc was launched, in 1992. The product was launched as a device, with clearance from Health Canada, and without preceeding clinical trials. John Feilders explains: “We built on the reputation of Healon and, furthermore, we had excellent relations with the Canadian authorities.”

The first distribution rights for Synvisc were sold to Syntex Pharmaceutical Intl. in 1993. Biomatrix received an upfront payment of 1 mUS$, and the distributor proceeded toward established markets in the UK, Ireland, France and Scandinavia. The deal presupposed Synvisc’s subsequent CE certification, which was obtained in November, 1995. In 1994, a new contract was signed by Biomatrix and Syntex Pharmaceutical Intl., now called Roche-Syntex. Roche-Syntex was awarded a number of new markets in exchange for payments to Biomatrix of 7 mUS$.

Distribution rights for Hylaform were signed in 1996 with Collagen Corporation, making it the market’s first hyaluronic acid-based dermal filler with CE certification. Biomatrix received an initial 5 mUS$ in return.

**Conflict settlement followed by termination of a twenty-five year collaboration**

During the spring of 1993, Endre Balazs initiated the audit of his royalty payments, as agreed upon during the 1992 negotiations with Kabi Pharmacia. From an early stage, his auditor discovered that Pharmacia (later Kabi Pharmacia), according to his judgment, had not made sufficient payments to Balazs. The result was an April, 1993 letter from Balazs’ attorney, sent to Ophthalmics Division CEO Toni Weitzberg:

”Although the audit to date has not been completed, it is nevertheless clear that Pharmacia failed to pay the correct amount of royalties to Dr. Balazs. The amount of underpayment is very significant, although the precise amount is presently being analyzed and some additional auditing may be required. Dr Balazs would be willing to discuss with you a possible amicable settlement of this claim. If you are not able to reach a settlement, however, this claim shall be settled by arbitration.”

Kabi Pharmacia responded by denying any wrongdoing with respect to royalty payments to Balazs. This marked the beginning of a drawn out legal process. Balazs felt forced to further his claim in court, and did so in 1994. The dispute was handled in Boston, Massachusetts, in accordance with the rules of the American Arbitration Association. In November, 1996 the parties finally agreed to a settlement. During the settlement process, Kabi Pharmacia went through different changes, including the merger with Upjohn, Inc. in 1995. The company Balazs finally settled with was therefore Pharmacia & Upjohn.
Root causes of the conflict

As stated in Part I, the license agreement between Biotrics and Pharmacia of January 1976 was preceded by three so-called options to license agreements and a license agreement of October 1974 which did not include USA, Canada and South Africa. In the final agreement, where the American market was included, the parties agreed to a royalty of 4.2 percent during a ten year period: "from the first commercial sale in each country.” In countries where valid patents existed, a royalty of 1 percent per year was to be paid from the beginning of the eleventh year until the expiration of the patent. The parties also agreed to an annual minimum royalty of 100,000 US$ during 1976-1985.

Pharmacia had, according to their opinion, paid annual royalties to Balazs in strict accordance to the agreement. However, their interpretation of the agreement differed substantially from that of Balazs. According to Pharmacia, the agreement specified that the minimum royalty should be replaced by the sales-based royalty as soon as sales exceeded 2,381,000 US$ (0.042 x 2,381,000 US$ > 100,000 US$). Sales had surpassed this milestone already during 1981.

Endre Balazs on the other hand, with support from his attorney, disputed Pharmacia’s interpretation of the agreement on two main points. First, Balazs was opposed to Pharmacia’s method of determining when a ten-year period had begun with respect to the introduction of licensed products on partial markets. Second, Balazs did not agree with Pharmacia’s interpretation of the concept “first commercial sale”. According to Pharmacia, the 1976 agreement made no differentiation between partial markets. One such example was the launching of Healonid Vet. in France in 1976. Due to this Pharmacia ceased paying royalties for France already in 1986, despite the fact that Healon was not introduced to the French eye surgery market until 1983. And on the American market, royalties were reduced to 1 per cent in April 1990, as Healon was introduced in the U.S. in April 1980.

Not until the audit at the onset of 1993 did Balazs realize that royalties had been prematurely minimized for certain countries. According to Balazs’ attorney, such action by Pharmacia was a breach of the agreement’s intention. In the opinion of Balazs, separate calculations should have been done for partial markets. According to this logic, royalties for the French market should have been paid well into the 1990’s, despite the fact that Healon was first introduced for veterinary use in France in 1976. In addition, Balazs did not agree with Pharmacia’s calculation of royalties for the American market. At the time of Healon’s release in the U.S. (April, 1980) there were no well-functioning production and distribution systems present. As a result, Balazs was of the opinion that Pharmacia should begin counting the ten-year period no sooner than such structures were in place. According to Balazs, “first commercial sale” on the
U.S. market did not take place until end of 1983. Balazs also disputed royalties for the Japanese market. Pharmacia ended royalty payments for Japan in 1992, although commercial sales of any significance had not begun until 1986, as it was then that Healon finally received approval from the appropriate Japanese authorities.

Pharmacia’s reply to Balazs’ claims was simple. There was no disputing the fact that a clause with respect to partial markets would have been beneficial for Balazs. However, there was nothing in the license agreement of 1976 to support separate royalties for partial markets. Pharmacia even admitted that sales-based royalties replaced the minimum royalty before proper production and sales structures were in place due to the great, and unexpected market success of Healon. Alternatively, Pharmacia could have continued to pay Balazs the agreed minimum royalty while waiting for such structures to take form. But this would have implied that Pharmacia would have withheld royalties which far exceeded the minimum royalty, a situation that, according to Pharmacia’s assumptions, Balazs at that point in time most likely would not have accepted.

**Settlement instead of arbitration**

Balazs and Pharmacia continued to meet in order to resolve the conflict. Both parties felt an increasing pressure to reach an agreement as the matter threatened to become costly as well as long. The dialogue itself took part in large between Endre Balazs and Göran Pettersson, who had recently been appointed Vice President and Head of Ophthalmology at Pharmacia & Upjohn.

It is evident from letters between the two that discussions regarding a settlement began at the beginning of 1996. In May 1996 Balazs expresses willingness to negotiate his demand of 15 mUS$, despite the fact that he, according to his own calculations, was owed more than 30 mUS$ in unpaid royalties. He writes:

”My willingness to accept only $15 million represent a substantial compromise. I see no reason to lower that figure, particularly since your only response to our meeting has been the suggestion that I revise my number to a clearly unacceptable single digit number. If you truly want to settle, you should come back with a more realistic approach.”

Balazs received no immediate response to the letter, at which point he sent a fax directly to Pettersson in August, 1996. Pettersson’s reply arrived within a couple of weeks:

”Although I disagree with the numbers in your fax, I indeed appreciate your suggestion to have our respective attorneys to meet in order to constructively explore the
possibility to reach a settlement. ... I am prepared to reconsider Pharmacia & Upjohn’s offer provided we arrive at a realistic sum. I am certainly not able to meet your previous indications for a settlement and I would expect that you too are willing to reconsider your position.”

A settlement was reached in November of 1996 in New York, at which time Balazs had further reduced his demand to 13mUS$. Pharmacia agreed to pay Endre Balazs 6.7 mUS$, 5.2 mUS$ of which represented unpaid royalties for the Japanese market during 1993-1996. Balazs was certainly not pleased with the outcome, but preferred not to push the matter further.

An unexpected termination

In an unexpected turn of events during settlement negotiations, Pharmacia & Upjohn notified Biomatrix that they were terminating the partnership for hylan fluid. The partnership had been agreed upon in 1992 and was to last well beyond 2000. The decision was explained in a letter to Endre Balazs from Göran Pettersson on July 4, 1996. Upon immediate termination, Pharmacia & Upjohn was obliged to pay 1 mUS$ in compensation to Biomatrix. Pettersson assured Balazs that the money would be transferred by July 8.

The move by Pharmacia & Upjohn to split with Biomatrix ended a nearly 25 year partnership around hyaluronic acid. Although the decision was quite unexpected, there was no panic at Biomatrix. To the contrary, Biomatrix was well on its way to realizing one of Endre Balazs’ largest dreams in establishing a leading product world-wide for treating osteoarthritis.

Broad success for Synvisc leads to sale of Biomatrix

Biomatrix strategy to sell distribution rights for Synvisc to different companies for different markets had attracted much attention throughout the pharmaceutical industry. As a result, companies were lining up in hopes of being able to purchase sales and distribution rights for the product. Balazs and his colleagues at Biomatrix were not slow to act. In 1996, Biomatrix cashed in 7 mUS$ and was promised milestone payments by Boehringer-Ingelheim France S.A. in return for sales rights. This contract was followed by yet another, this time between Biomatrix and Wyeth-Ayerst in 1997. The agreement was timely for both the American distributor and for Biomatrix, as Synvisc had just received FDA approval. As was the case with Healon, the key was applying for Synvisc’s approval on the basis of a medical device and not a
pharmaceutical. The agreement with Wyeth-Ayerst led to initial payments of 19 mUS$ for Biomatrix.

During the rest of 1997, Biomatrix maintained its momentum. It sold sales and distribution rights in excess of 100 mUS$. The level of achievement experienced by Biomatrix led to rapid expansion of the company. A new production plant was built in Ridgefield, New Jersey and the number of employees rose from 180 to 369. On July 23, 1998, Biomatrix was assigned the abbreviation BMX as it was introduced onto the New York Stock Exchange in a truly landmark occasion.

The rapid expansion of Biomatrix continued during 1999. Product sales increased from 37.8 mUS$ in 1998 to 72.0 mUS$. This was primarily due to increased sales of Synvisc in the US and Europe coupled with the launch of Synvisc in Australia, New Zealand, South Africa and certain Southeast Asian markets. The company was listed by Fortune’s magazine as one of the 100 fastest growing companies in the U.S. The number of employees increased to over 400 and the price of a Biomatrix share at the NYSE had at the end of the year risen above 20 US$. Endre Balazs commented on his company’s development as follows:

“Biomatrix closed the century with its strongest showing to date, proudly announcing its fourth consecutive year of profitability. The opening of the company’s U.S. manufacturing facility allowed us to provide our worldwide marketing partners with enough products to meet the demand for Synvisc. This allowed our U.S. marketing partner, Wyeth-Ayerst, to start its first direct-to-consumer advertising campaign in July 1999, which boosted end user sales approximately 50% from the first half of 1999 to the second half of 1999. … We look forward to 2000 being another positive year for the company as we work to increase the global market penetration of Synvisc, Hylaform, and Hylashield®, launch new products in the US and Europe, and accelerate our efforts to initiate and complete clinical trials of our new viscoelastic medical therapeutic devices.”

At the age of 79, Balazs felt like the time was right to sell Biomatrix. His wife, Janet Denlinger felt the same. The biotech company Genzyme Corp. had courted the company readily, amongst others. Biomatrix entered into negotiations with Genzyme in 2000. On March 7, The New York Times declared: “The Genzyme Corporation said yesterday that it had agreed to acquire Biomatrix Inc. for about $738.5 million in cash and stock.”

The article also gave the following account: “Under the terms of the deal Biomatrix shareholders will receive either $37 in cash or one share of the newly created Genzyme Biosurgery stock for each Biomatrix share. The cash portion of the deal is limited to
$245 million; if the cash choice is oversubscribed, Biomatrix shareholders will get part cash and part stock.”

The terms of the agreement would prove to be less favorable than anticipated for many of Biomatrix shareholders. At the time of the sale, Endre Balazs and Janet Denlinger owned slightly less than 30% of Biomatrix. Part of the payment they received was in the form of Genzyme Biosurgery stocks. As for the rest of Biomatrix employees, those who chose or otherwise felt obliged to accept payment fully in stocks were hit much harder. What provoked their misfortune was the value of the newly formed Genzyme Biosurgery’s tracking stock plunging on the market after the sale.
CHAPTER 16: In the wake of success: Three unforeseen legal disputes

Genzyme’s purchase of Biomatrix in 2000 did not lead to the rest and relaxation that Endre Balazs and Janet Denlinger had hoped for, at least not immediately. The reason for this was being involved in no fewer than three legal disputes connected to the sale of Biomatrix. In two of the cases, Balazs and Denlinger were plaintiffs, assuming the role of defendants in the third.

The first dispute: Small stockholders in Biomatrix accuse company leaders and owners of manipulating stock prices

In July 2000, a class action lawsuit was brought before a U.S. District Court in New Jersey. The suit was initiated by a group of small stockholders who had lost money on stock acquisitions during the period July 20, 1999 – April 25, 2000. Biomatrix, Inc. stood accused of wrongdoing as well as did Endre Balazs and Rory Riggs in their respective roles as owner and chief business officer.

In the suit, Balazs and Riggs were accused of exaggerating financial results from late 1999 and early 2000, thus inflating the company’s economic well-being. Their motivation, according to litigators was to push company stocks to their limit preceding the sale. The price of a Biomatrix share was just over 20 dollars per share on January 3, 1999. As fourth quarter results were presented on March 1 of the same year, stocks had soared to 37 dollars per share.

On March 7, details of the purchase were made public. Genzyme had agreed to purchase Biomatrix Inc. for 738.5 mUS$. Stockholders were offered 37 US$ per stock, but only up to 28.38% of the sales price for the company itself. The remaining 71.62% were paid by exchanging Biomatrix stocks for those of Genzyme Biosurgery, a newly formed tracking company within Genzyme. Also part of the same tracking company were Genzyme Surgical Products and Genzyme Tissue Repair. For Endre Balazs and Janet Denlinger, the deal meant 70 mUS$ and 4.8 million stocks in the new company. Rory Riggs received 18 mUS$ and 1.2 million stocks in Genzyme Biosurgery.

By April 25th of the same year, stocks in Biomatrix had fallen to under 20 US$ per share, the result of poor first quarter sales. Those who had been enticed to buy stocks after Genzyme had announced its purchase of Biomatrix saw the value of these shares nearly halved.
Not only did the class action suit allege manipulated sales numbers; one example being accusations of channel-stuffing in the case of sales to American licensee Wyeth-Ayerst Laboratories, but also even claims that the therapeutic effects of Synvisc were fabricated. Balazs and Riggs denied any wrongdoing with regard to all of the charges against them and actively worked toward a settlement.

After two years of negotiations, the New Jersey District Court announced that the parties had reached a settlement. Biomatrix agreed to pay compensation to stockowners in the amount of 2.45 mUS$. The amount was applied to approximately 8.7 million stocks, leading to a mere 28 cents per stock after legal fees had been paid. It was but little consolation for stock buyers who had invested in Genzyme Biosurgery as the sale of Biomatrix was announced. On November 27, 2002, a day before the settlement was reached, Genzyme Biosurgery stocks were at 3 dollars, less than a tenth of the value of Biomatrix stocks two and a half years prior.

The second dispute: Genzyme Biosurgery stockholders claim deception by Genzyme

The second dispute was a result not of the sale itself, but rather Genzyme Biosurgery’s dramatic stock devaluation. Previous Biomatrix stockholders, now owners of stock in Genzyme Biosurgery, initiated a class action lawsuit in August 2003 against Genzyme. This time, stock owners were represented by the previously accused Rory Riggs, former president of Biomatrix, and John Lewis, president of Gardner Lewis, a money management firm and one of the largest shareholders in Genzyme Biosurgery.

As mentioned earlier, the price of a Biomatrix share was 37 dollars at the time Genzyme’s purchase of the company was announced. Stocks in Genzyme Biosurgery, given to Biomatrix shareholders after the sale, had dropped to 2.57 US$ by the spring of 2003. According to the class action suit, the falling stock price was a direct result of intentional manipulation by Genzyme, in an attempt to reacquire Genzyme Biosurgery as cheaply as possible. Critics pointed to the fact that Genzyme executives had large amounts of stock in the parent company and modest holdings on Genzyme Biosurgery shares. Obtaining undervalued stock in Genzyme Biosurgery was therefore a very lucrative transaction.

With support from the contract regulating Genzyme Biosurgery’s status as a tracking company, the 2.57 US$ Genzyme Biosurgery shares were able to be re-purchased for a mere 1.77 US$ per share. This so-called forced buyback was announced on May 8, 2003. For those Biomatrix shareholders who had neither received compensation after Genzymes' acquisition of Biomatrix, nor sold off their shares during the process itself, this was a catastrophic development. For example, a shareholder with 1000 shares of
Biomatrix stock, worth 37,000 US$ in March 2000 were now forced to sell for 1,700 US$.

As in the previous case, Genzyme executives denied any wrongdoing. After five years of negotiations, a settlement was reached in January 2009. Genzyme agreed to pay 64 mUS$ in compensation, which meant very little for each shareholder. In total, 3.35 US$ per share was paid out after legal and court fees.

The third dispute: Defamation campaign against Endre Balazs and Janet Denlinger

During the course of the Biomatrix sale, Endre Balazs and Janet Denlinger were made aware of a defamation campaign being waged against them on the Yahoo Finance Message Board. Balazs and Denlinger initiated a so-called John Doe lawsuit in January 2000 and a New Jersey Superior Court ruled that the matter would be decided by a summary judgment. On August 2, 2000, the court reported that it had found three individuals, two of which were employees of Biomatrix, and the third, twin brother of one of the employees, guilty of defamation.

An investigation revealed that from April 1999 until August 2000, the three individuals had posted over 16,000 messages on the Yahoo Message Board, using 23 different pseudonyms. Among unsubstantiated allegations that had been made were:

- that Synvisc produced harmful side effects
- that Biomatrix covered up negative financial and product information
- that Biomatrix and its corporate officials had connections to the mafia
- that the merger between Biomatrix and Genzyme was a ploy and would never take place
- that the CEO of Biomatrix was under investigation for crimes committed during the Second World War
- that a top level Biomatrix corporate officer routinely sexually harassed employees

Although all of these allegations were successfully refuted during legal proceedings, it was quite probable they caused Biomatrix economic harm. During the period in which the messages appeared on the Yahoo Finance Message Board, Biomatrix’ stock dropped from 35 US$ per share to 21 US$.

The identification of the three individuals behind the smear campaign was made possible by Biomatrix petitioning the court to subpoena Yahoo to identify the authors of the defamatory messages, with which Yahoo complied.
The court’s ruling on the case received widespread attention in the media. In an article in the Wall Street Journal on August 3, 2000 with the heading: "Judge Rules Online Postings About Biomatrix Were Libel", reference is made to two legal experts who say that the case is the first time a court has found that an individual’s online postings constituted libel. "Companies nationwide have brought more than 100 such cases, but the suits are usually settled out of court before a judge can rule.” A lawyer representing a firm that had represented several companies in cyber smear cases said: "This ruling sets a precedent, and I suspect lawyers across the country will be banging on the clerk’s door to read it.”

In his comment on the case, Endre Balazs referred to the victory as "bittersweet":

"While we are pleased to be vindicated by this favorable judgment, the victory is bittersweet. Regrettably, our company, its employees, technology, and lead product were seriously maligned and suffered at the hands of a few malicious detractors. We are proud that Biomatrix is one of the first companies to succeed in pursuing such litigation to summary judgment, and remain committed to upholding the integrity and reputation of Biomatrix, its employees and its products. We will continue to defend vigorously against attacks."
CHAPTER 17: What became of Synvisc?

Synvisc sales continued to increase in the hands of its new owner, establishing Genzyme\(^\text{24}\) as one of the world’s four leaders within the “viscosupplementation” market. Genzyme was accompanied by the Japanese companies Seikagaku, proprietors of Supartz and Gel-One, Chugai, (owned by Roche) and the Italian competitor Fidia Farmaceutici with their Hyalgan and Hyalubrix. Notably, the company Endre Balazs referred to in his February 1988 letter to Erik Danielsson as having launched a hyaluronic acid-based product for osteoarthritis was none other than Seikagaku.

During the period 2001-2008 global annual sales of Synvisc increased from 83 mUS$ to 263 mUS$. An important milestone in the development of Synvisc was the introduction of Synvisc-One – in Europe in 2008 and in the US in 2009 – which is a single-dose injection claiming to provide up to six months of osteoarthritis knee pain relief. Global sales of Synvisc and Synvisc-One went from 328 mUS$ in 2009 to 482 mUS$ in 2013.

According to a market survey by Millennium Research Group Inc, the global hyaluronic acid viscosupplementation market generated 1.76 billion US$ in sales during 2012. The American market was responsible for 41.2 percent of total sales, Europe for 7.8 percent and Asia Pacific (including Brazil) for 51 percent. Leading global sales was Seikagaku, with 29.4 percent. Sanofi/Genzyme (Synvisc and SynviscOne) generated 26.8 percent of the market and lastly came Chagai and Fidia at 11.8 percent and 7 percent respectively. The low figure for Europe can be explained by the fact that in most European countries treatment of knee disorders with medical devices based on hyaluronic acid is not eligible for reimbursement.

As mentioned above, total sales of Synvisc and Synvisc-One in 2013 were 482 mUS$. This can be compared with another product that also has Endre Balazs as its “father”, namely Healon. The “all time high” for Healon was reported in 1993, when total sales reached approximately 220 mUS$. Despite seemingly impressive sales figures, they will be far surpassed by those products discussed in the two following chapters. Notably, the products in question can also be linked to Balazs in one way or another. The first of which, Xalatan, whose coming into being is discussed in Part IV, became the first blockbuster ever (i.e. annual sales exceeding 1 billion US$) within eye medicine. The birth of the second product, or rather product group, dermal fillers, is the focus of Part V of this book.

\(^{24}\) Since 2011 owned by Sanofi
CHAPTER 18: The project no one wanted

“Sweden’s missed opportunity,” read the headline of the April 12, 2005 article in the Swedish business magazine Affärsvärlden. The writer of the article, Lars-Erik Bränfeldt, was referring to Xalatan, world leading medicine for glaucoma treatment, earning American-based Pfizer over a billion US$ a year. Originally introduced by Pharmacia-Upjohn in 1996, Xalatan’s Swedish life was short, essentially ending when Pfizer took over Pharmacia Corp. in 2003. All the painstaking groundwork leading up to Xalatan’s release, which took about ten years, was performed in Sweden under leadership of Finnish pharmacologist Johan Stjernschantz. The patent, however, on which the development work was based was U.S. patent 4599353, “Use of eicosanoids and their derivatives for treatment of ocular hypertension and glaucoma”, the existence of which could be attributed to Hungarian-born researcher László Bitó at the Department of Ophthalmology Research Division, Columbia University.
László Bitó was born in 1934. He fled to the U.S. in 1956 in the wake of the Hungarian revolution. His limited knowledge of English prevented him from studying what he most desired, namely literature. However, his knowledge of Latin steered him toward biology and medicine. After first studying at Bard College in Annandale-in-Hudson, New York, Bitó would later attend Columbia University where he obtained his Ph.D. in 1966 in cell biology and biophysics. After two years as post doctoral student he started his research career at the Department of Ophthalmology at Columbia University.

László Bitó stubbornly hangs on

At an early stage, Bitó was fascinated by the possibility of treating glaucoma with the help of prostaglandins. Prostaglandins are hormone-like substances found in a number of the body’s organs. Glaucoma is a serious eye disease that affects the optic nerve and damages one’s field of view. The disease becomes more likely with age and is one of the leading causes of blindness. More often than not, glaucoma causes an increase in the natural pressure within the eye. The most common form of the disease is called “open angle glaucoma”. Globally, more than 60 million people suffer from glaucoma.

László Bitó hypothesized that prostaglandins could be used to decrease pressure in the eye in glaucoma patients. He believed that they would increase the flow of the aqueous humor, thus relieving pressure caused by glaucoma. If proven, his theory would revolutionize glaucoma treatment worldwide. However, Bitó met much resistance among his fellow prostaglandin researchers. Many researchers were convinced that prostaglandins would in fact only aggravate the problem of elevated pressure in the eye. The uncertainty of his peers would prove to be a major obstacle for Bitó as he eventually submitted a patent application and began searching for licensees. Despite active backing by the newly opened Office of Science and Technology Development (OSTD) at Columbia University, American pharmaceutical companies were largely uninterested. It was during this time that Bitó began thinking of his friend and colleague Endre Balazs at the Department of Ophthalmology. Balazs had achieved much success by developing and later introducing Healon onto the eye surgery market in cooperation with the Swedish pharmaceutical company Pharmacia.

As no fewer than three separate American companies declined to take on Bitó’s prostaglandin project, he and OSTD were free to solicit non-American pharmaceutical companies. Furthermore, Bitó was allowed to negotiate with pharmaceutical companies personally after twelve months’ time, a fact brought to his attention by Balazs. Future sales resulting from a manufacturing agreement signed within one year of the patent application would have greatly benefited Columbia University, as part of
an 80/20 scheme, the majority of which going to Columbia. Bitó and Columbia had collectively attempted to find a willing partner for some ten months, meaning that after two more months Bitó would be free to solely reap the benefits of his labor. Endre Balazs advised László Bitó to wait a couple of months and offered to help him with business contacts once Columbia University was no longer in the picture. Bitó did not agree to the arrangement put forth by Balazs, as he preferred to work together with OSTD. His reasoning was based on a complete lack of interest for the commercial development of his project. He saw it as a mere necessary evil enabling him to continue with his research. If OSTD managed a successful commercial introduction, Bitó would be able to continue doing what he loved while cashing in 20% of future royalties.

As Bitó explained his stance to Balazs, he also wondered if Balazs would be willing to put him in contact with Pharmacia nevertheless. In a written description of the events, Bitó writes:

"Thus I asked Endre Balazs, that instead of what he advised me to do – and offered to help with – to put me in touch with the president of the company, Pharmacia, that entered the eye field not long before very successfully with Healon."

When I interviewed László Bitó in Budapest in July, 2013, he could not recall his first contact at Pharmacia, but whoever it was, that person connected him with Bengt Ågerup, the CSO of Pharmacia Ophthalmics.

Though Xalatan has nothing in common biochemically with hyaluronic acid, its future commercial success was owed largely to Healon. Had it not been for Endre Balazs’ business relationship with Pharmacia, the company would never have been offered partnership with László Bitó as part of his prostaglandin project. However, it would be incorrect to describe the benefit as anything but mutual. Had it not been for Pharmacia, it’s not certain that Bitó would have found a partner elsewhere. Carl Camras, a close colleague of Bitó’s, described the situation as follows:

"If László Bitó’s friend hadn’t done wonders for Pharmacia, no one would have picked it up."

Further highlighting the universal benefit of the Bitó – Pharmacia cooperation, it was Pharmacia’s unique knowledge and experience of the eye market that enabled them to recognize the commercial potential of Bitó’s research. This knowledge and experience had been a direct result of the company’s work with Healon. It is for these reasons that Xalatan deserves substantial attention in a book about “The Magic Molecule.”

This part of the book will be dedicated to illustrating Xalatan’s development from the perspectives of both Pharmacia/Pfizer and László Bitó. How could Pharmacia invest in a project that had been uniformly dismissed by leading American pharmaceutical
companies? The process itself will also be examined, one which resulted in one of the biggest and most profitable products in history within the ophthalmic market. And what role did László Bitó play? And how did Xalatan’s release impact Bitó’s life?
CHAPTER 19: The Xalatan saga from different perspectives

Let us for a moment travel back in time to the end of 1982. Despite Healon’s introduction to the American eye market not even three years prior, it had risen to the ranks among Pharmacia’s most valuable products, with annual sales approaching 20 mUS$. The American market for lens implants had exploded, seemingly the result of Healon’s introduction. During 1982 alone, more than 400,000 such surgeries were performed in the U.S. and increases were expected there as well as in Europe and Japan.

In an effort to offer customers a complete package for lens implants, Pharmacia had acquired a Dutch manufacturer of intraocular lenses named Medical Workshop B.V. Pharmacia thus gained the capability to offer both intraocular lenses and the ophthalmic viscoelastic device necessary to perform a transplant. Though the venture was a success, Pharmacia Ophthalmics’ CEO Hans Åkerblom and their CSO Bengt Ågerup were not entirely satisfied. Given the qualified network of researchers and sales representatives they had managed to build up, the two had larger plans in mind with regard to increasing Pharmacia’s product portfolio within the eye market. The subsequent plan of action was described by Lars-Erik Bränfeldt in an April 2005 article in Affärsvärlden:

“Bengt Ågerup received a tip that a friend to Endre Balazs had a number of projects underway within the area of eye research.”

According to the article, Ågerup then proceeded to examine Bitó’s projects when one in particular caught his eye. The particular project that sparked Ågerup’s interest was one dealing with a possible glaucoma treatment. The article paints a picture of Bitó having had a broad portfolio of projects, one of which was pursued by Pharmacia. However, this was not the case. Bitó’s prostaglandin project was his only undertaking, and was the result of his entire research career.

Shortly after Ågerup became aware of Bitó’s work, he set off for Columbia University, first on his own, and later accompanied by Pharmacia Ophthalmics’ CEO Hans Åkerblom. Only a short time later negotiations between Pharmacia and OSTD took place, and an agreement was signed. As a result, Pharmacia was awarded commercial rights to Bitó’s prostaglandin project worldwide, based on the previously submitted patent application. Columbia University was paid an up-front advance in the order of 150,000 US$. Pharmacia also agreed to pay 4% royalties on future sales. The 4% portion would be divided between Columbia University and Bitó, 80% going to Columbia University. Bitó was free to do as he wished with his 20%.
A project without support risks falling through the cracks

The prostaglandin project got off to a rather slow start at Pharmacia. The situation could at least partially be explained by the conflict between Bengt Ågerup and newly appointed CEO Jan-Erik Engkvist. The falling out between the two is described in Chapter 11. It would last from Engkvist’s first day on his new post until Ågerup’s departure from Pharmacia some 15 months later, in December 1984. Despite initial difficulties, Ågerup managed to hire two key individuals for work on the prostaglandin project. Helen Backlund joined on as project leader and Bahram Resul was brought onboard to use his knowledge of the chemistry involved in transforming Bitó’s patent to a finished product.

A few months after Bengt Ågerup’s departure, Helen Backlund was relieved of her duties as project manager at the request of Jan-Erik Engkvist. Backlund and Ågerup would later marry.

Support within Pharmacia Ophthalmics for the prostaglandin project was very weak after the departures by both Hans Åkerblom and Bengt Ågerup. There was even growing doubt about Bitó personally and the entire venture was threatened on a number of occasions, a fact also mentioned in the article in Affärsvärlden referred to above. These sentiments are not confirmed by Jan-Erik Engkvist. Rather, Engkvist insists that the two individuals hired to replace Ågerup arrived without delays as not to disrupt business any more than necessary. Specifically, he claims that research manager Gösta Jonsson and product development manager Johan Stjernschantz had taken their places a mere three months after Ågerup’s exit. According to other sources, however, Stjernschantz was not hired until January of 1986, a full year later.

Obviously, Bitó himself was alarmed during this uncertain period and encouraged OSTD boss Jack Granowitz to contact Pharmacia in an attempt to revive the project. Granowitz did so by letter during the autumn of 1985. Columbia University was quite unhappy with the lack of attention being afforded the project and reminded Pharmacia that there was legislation in place that would allow for removal of the project in the event of continued inactivity.

Rejuvenation at the hands of new project leader

New product development manager Johan Stjernschantz’ first item of business involved a recommendation regarding the future of the prostaglandin project. Stjernschantz was convinced of the project’s potential and recommended that it be furthered. He also knew that the project would not succeed on potential alone and was convinced at an early stage that the venture would require a large, sustained effort. To
this end, Stjernschantz asked to be excused of duties as Pharmacia Ophthalmics’
product development manager in order to fully devote his time to the prostaglandin
project. His request was granted along with additional financial support just under one
million US$. The funding was to be spent on building a laboratory and employing a
group of people focused solely on transforming Bitó’s patent into a successfully selling
product.

The trust and responsibility placed upon Stjernschantz by Engkvist was quite big. Stjernschantz was given nearly total freedom within the framework of the project and its goal. The result was a sort of miniature company within Pharmacia. The project had its own chemistry department, preclinical and clinical trials divisions and registration department. There were some 70 individuals employed within the project at one point. Stjernschantz himself was described as a “lone wolf, obsessed with the idea of producing an effective pharmaceutical product,” according to the earlier mentioned article in Affärsvärlden, which continues: “He was very thorough and not slow to scrutinize his own findings. He was a reserved type who felt most at home in the lab. His conservative handling of funds made him popular with his employers.” It is even claimed that Stjernschantz used himself for testing. A person involved in the project early on describes how progress could be seen in Stjernschantz’ eyes. As the redness in his eyes dissipated, everyone knew that headway was being made.

A breakthrough – the discovery of latanoprost

A major breakthrough in the prostaglandin project was experienced around 1990 at the
hands of Johan Stjernschantz, Bahram Resul and colleagues. They had successfully
created a so-called prostaglandin analog (F2α-analog) with the pressure-reducing
properties they had hoped for. Furthermore, they had successfully avoided the side
effects earlier experienced with Bitó’s prostaglandins. The analog was given the
generic name latanoprost. There were two names listed under "originators" on the
patent application for latanoprost, neither of which was László Bitó. Rather, it was
Johan Stjernschantz and Bahram Resul who were notified in March, 1994 that their
application had been successful. Despite the rather quick turnaround regarding a
patent, obtaining FDA approval would prove to be a much more significant challenge.

The onset of 1991 marked an unexpected and alarming discovery that threatened the
totality project. Stjernschantz’ team discovered discoloration in the eye of a monkey
used in testing the product. The monkey’s iris had turned dark brown and it was feared
that the underlying problem was malignant melanoma. If indeed melanoma had been
caused in one of the test animals, the project would be abandoned at once. Intense work
began immediately at Uppsala University and Columbia University to determine the
reason for the discoloration. Ultimately, both facilities determined that the phenomenon was not a symptom of cancer. However, the issue would later turn up in clinical trials involving humans, creating the very difficult task of convincing FDA that despite this, there was no medical danger caused by the product itself. The explanation eventually accepted by FDA was largely summarized in FASS ("Pharmaceutical Specialties Sweden") under the heading Xalatan: "Very common side effect (more than 1 in 10 users), is brown pigmentation of the iris. Most likely to occur in patients with mixed eye color rather than those with distinct solid colored iris. Discoloration of the iris can take several years but usually begins within 8 months of treatment. Changes in color can be permanent and are more obvious if Xalatan is used in only one eye. No medical concerns are associated with discoloration. Further discoloration ceases as treatment with Xalatan is ended."

Pharmacia and Upjohn merge – consequences for Xalatan

A merge involving Pharmacia and Upjohn took place during the late autumn of 1995, approximately six months before Xalatan would receive FDA approval. At a glance, the merger appeared to benefit the Xalatan project as Upjohn was a world leader within research and development of prostaglandins. However, Upjohn was well aware of the attempts underway to treat glaucoma with prostaglandins, and they were skeptical. In fact, the company had been among those approached by Columbia University some years earlier as a possible collaborator on Bitó’s project. Then they had declined.

Upjohn had a long-standing collaboration with Swedish researchers Sune Bergström and Bengt Samuelsson. During the 1950’s, Bergström had been awarded a significant research grant, and Samuelsson was involved in four patents granted to Upjohn during the 1970’s. Together with American John Vane, the trio was awarded a Nobel Prize in 1982 for: “… their discoveries concerning prostaglandins and related biologically active substances.”

At the time of the Pharmacia and Upjohn merger, Samuelsson was a member of Pharmacia AB’s board, as he had been since 1983. His board membership was largely attributed to Bengt Ågerup, according to the aforementioned article in Affärsvärlden. Samuelsson would also agree to sit on the board of Pharmacia & Upjohn.

A possible explanation for Upjohn’s reluctance to take on Bitó’s project was an apparent fear of damaging prostaglandins’ standing within other areas of treatment. In fact, there had been doubt within Upjohn since the early 1980’s regarding the future of

prostaglandins within medicine. According to the website “Memories of the Upjohn Company” \(^{26}\), Upjohn’s substantial efforts within the area of prostaglandins is described: ”It was anticipated this class of molecules would have many applications and be highly profitable. Sadly this did not happen – the few prostaglandin products from this effort never even repaid the money spent on developing them.”

The negative experiences at Upjohn with prostaglandins likely even resulted in the unexpected response that followed FDA approval for Xalatan in June 1996, according to the article in *Affärsvärlden*. Instead of renewed energy with regard to the Xalatan project, it was downgraded in order to benefit other ventures. Stjernschantz, Resul and a few others of their research group left Pharmacia & Upjohn at the beginning of 1997 and became employees of Uppsala University. Their former employer provided them with a research grant that financed their research for another couple of years.

In the previously mentioned article in *Affärsvärlden*, Johan Stjernschantz expresses his disappointment:

”My hope was that we would create a world leading company in ophthalmology. It was strange that we weren’t given the opportunity to continue.” He continues: ”The original idea was that we should develop a second generation of Xalatan and also start working with other indications. But the merger with Upjohn resulted in new priorities for our research, and the management wanted to shut down the research on prostaglandins. When they discovered that Xalatan was on its way to become a big success they realized that a certain research effort was needed. That’s why we could continue with our research at the university for a while.”

The picture of the project conveyed by the article in *Affärsvärlden* is not confirmed by Göran Ando when we talk in August 2014. At the time of FDA’s approval of Xalatan in June, 1996 he was Executive Vice President of Pharmacia & Upjohn, responsible for research as well as product and business development. Ando is, in January 2015, among other things, chairman of the board of directors of the Danish pharmaceutical company Novo Nordisk A/S. According to Ando, the top management of Pharmacia & Upjohn at that time was fully determined to pursue established plans for Xalatan on the ophthalmology market. The researchers, on the other hand, wanted to extend the research on prostaglandins to cover also areas that were not among the intended core activities of the company. A consensus agreement was therefore reached, according to Ando, implying that the researchers were transferred to Uppsala University where they were given the opportunity to conduct research under less restrictive conditions, supported financially by Pharmacia & Upjohn.

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\(^{26}\) http://www.upjohn.net/
Xalatan’s global conquest

As Stjernschantz alluded to in the interview above, the response following Xalatan’s introduction exceeded all expectations. As the product took the market by storm, sales reached 30 million US$ by the beginning of 1997. The following was written in Pharmacia & Upjohn’s annual report for 1996:

“The release of Xalatan in the United States, Switzerland and Sweden in 1996 has instilled hope in glaucoma sufferers. Though currently used as a secondary treatment option, the unique effects of Xalatan are unprecedented. Demand for the product continues to increase, thus adding to Xalatan’s future importance for patients and that of Pharmacia & Upjohn.”

The anticipation that was built up at the time of Xalatan’s release had been realized. It reached the list of top ten products sold by Pharmacia & Upjohn after the first full year of sales in 1997. Sales by year’s end amounted to 165 mUS$, earning a ninth place finish on the list. Notably, Xalatan’s cousin if you will, Healon, was the tenth best seller the same year. Due to falling prices and increased competition, Healon was losing ground. CEO Fred Hassan’s comment on Xalatan in the 1997 annual report read:

“Xalatan, our preparation for glaucoma treatment, has lead the American market since its introduction in 1996. Sales are expected to continue to rise as Xalatan is set to be released in all of Europe during 1998.”

The table below illustrates sales development of Xalatan from its release in 1996 until 2013. From 2001 and onwards the figures include also sales of Xalacom outside the U.S., a combination of Xalatan (latanoprost) and timolol. The product was never approved by FDA. Key events during the seventeen-year period are:

1. In 2000, Pharmacia & Upjohn merged with Monsanto and Searle, adopting the name Pharmacia Corp
2. Primary treatment approval for intraocular pressure is obtained by FDA in December 2002
3. 2003 marks Pfizer’s purchase of Pharmacia Corp
4. Exclusive market standing is lost in Japan and Italy in 2010
5. Exclusivity is lost in the United States in 2011, opening the door for generic latanoprost options
6. The same fate meets Xalatan the same year in 15 European countries
As evident by the table, Xalatan had its first blockbuster year in 2003, coinciding with Pfizer’s purchase of Pharmacia. The product continued to sell in excess of 1 billion US$ until losing exclusivity in 2011 as a result of patent expiration. From 2011 until 2013, no fewer than six companies have had generic latanoprost approved for use by FDA, among them Akorn, Alcon, and Bausch and Lomb. Similar developments have occurred in Europe and Asia. In an attempt at remaining competitive, Pfizer has had to drastically decrease prices. Combined with shrunken sales volumes, total sales have also declined significantly. Global sales of Xalatan in 2013 reached 589 mUS$, roughly half of what was experienced in 2010.

Regarding royalty revenues, there are alternative scenarios. Royalties of approximately 4% were paid either until 2007, the year in which Bitó and Columbia’s last supplemental patents expired, or until 2011, when the latanoprost patent expired. It is

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*Sales of Xalatan/Xalacom 1996-2013 (mUS$)*

_Source: Annual reports, Pharmacia & Upjohn, Pharmacia Corp., Pfizer_
also assumed that Bitó was paid one fifth of the 4% annually. During 1996-2007, Xalatan generated 405 mUS$ in royalties, of which 324 mUS$ were paid to Columbia University and 80 mUS$ to László Bitó. If royalties were in fact paid out until 2011, Columbia University would have received some 532 mUS$ compared to Bitó’s 133 mUS$.

**Xalatan, a “self-playing piano” or the result of clever marketing?**

**Success according to the researchers**

Xalatan’s wave of success can be attributed to opposing factors depending on who one asks. Bitó and his fellow researchers likened Xalatan to a self-playing piano from the time of FDA approval and subsequent release in the United States. Bitó began early to lecture in conjunction with conferences and symposia arranged by ARVO (Association for Research in Vision and Ophthalmology) and ISER (International Society for Eye Research), the latter society started by Endre Balazs in 1967. Bitó would later appear numerous times before the international community of experts on glaucoma together with Johan Stjernschantz. By the time Xalatan was approved by FDA and ready for sale, potential customers were well informed and eager to purchase. As one representative for the research team explained, Pharmacia’s marketing department assumed a lesser role than had been experienced as Healon was released. In the case of Xalatan, it was the responsible researchers themselves who built up and maintained a working relationship with the most renowned physicians in the sphere of Xalatan interest.

**Success according to the market strategists**

Given the tedious groundwork performed by László Bitó, and Johan Stjernschantz and his team, it would have been difficult not to have achieved a successful marketing campaign surrounding Xalatan’s release, according to Lena Kajland-Wilén, head of marketing for Xalatan from 1995-1997. However, the sheer scope of success enjoyed by Xalatan would likely not have been possible without a well-executed marketing strategy leading up to the release.

When talking to Kajland-Wilén in August 2014, she points out three important factors with regard to Xalatan’s market boom. First, a precise price strategy was employed. Second, the “Strategic Product Plan,” authored by her and three colleagues in the marketing department at the beginning of 1997 was instrumental in selling the strategy itself and keeping it on track. Lastly, Xalatan’s market prosperity was made possible by the strong relationship established between the marketing department in Uppsala and Upjohn’s former head office in Kalamazoo, Michigan, where the bulk of
responsibility was placed on preparing Xalatan for the market release on the U.S. market.

The price strategy itself was subject to much consideration and debate. Originally, Pharmacia & Upjohn was under the impression that Xalatan might in fact receive FDA approval as a “first line treatment,” meaning it would be among the short list of first choice treatment options. In this case, charging a price in line with that of market leading competitors would have been justified. This would have meant charging approximately 5 US$ per bottle. However, Lena Kajland-Wilén and her colleagues soon came to realize that approval as first line treatment was unlikely, which was eventually confirmed upon subsequent FDA approval. “Second line approval” meant that doctors would mainly use Xalatan in the event of particularly difficult cases of glaucoma, when no other medicines seemed to be effective. Price sensitivity can be expected to be much lower for this type of last resort medicine than first line treatments. Following this reasoning, Kajland-Wilén proposed a drastic increase in the introduction price of Xalatan. She suggested that the price be changed from 5 to 30 US$ per bottle. Her strategy was considered and later approved by Pharmacia & Upjohn executives and resulted in a very high profitability from the onset.

The Strategic Product Plan laid the groundwork for a consistent marketing strategy on a global scale. Xalatan and its medical advantages were promoted and marketed in the same manner in every country, and with the same central goal in focus. This enabled the best possible likelihood of Xalatan becoming a world leading product in glaucoma treatment. A main component of the marketing plan was first to succeed in establishing Xalatan as a “second-line treatment.” This would enable Xalatan to be proven on the toughest cases of glaucoma, after other treatments had been exhausted. If this went as planned, it would lead to eventual “first-line treatment” status.

Yet another important part of Xalatan’s global prosperity was winning the first and largest market, namely, the United States. A number of new challenges were encountered in achieving this goal. It was no longer Pharmacia Ophthalmics’ subsidiary in Pasadena, California that would be handling the introduction. Rather, it was Upjohn’s marketing department in Kalamazoo, Michigan. Located 250 kilometers west of Detroit, the marketing team in Kalamazoo was under the influence of different cultural and professional perspectives than those Pharmacia had grown accustomed to in California. With regard to quickly establishing a meaningful working relationship between the representatives in Sweden and Kalamazoo, the experiences gained from earlier work on Healon on the U.S. market were vital.
Or was it success thanks to the merger?

The merger between Pharmacia and Upjohn is discussed in the aforementioned article in Affärsvälden with respects to its contribution to Xalatan’s fate. A person with a long history within the eye division was quoted as saying: “Xalatan would have never reached such heights without the marketing muscle employed. Without the creation of Pharmacia & Upjohn and the unclouded vision of CEO Fred Hassan and research manager Göran Ando, it would not have become a blockbuster.”

When asked of the possible magnitude of Xalatan without the fusion, the same official replied: “maybe half as large.”

This sentiment was partially dismissed by article author Lars-Erik Bränfeldt. The “old” Pharmacia had indeed shown significant marketing know-how when it came to Healon. The number of doctors worldwide who treat glaucoma was, in fact, much larger than those who perform lens transplants, but the task of managing Xalatan would have been fully reasonable under Pharmacia’s leadership. In addition, Pharmacia’s strong standing within the eye market should not be downplayed in the case of Xalatan.
CHAPTER 20: László Bitó – the man who pushed on despite his critics

László Bitó can be described as the author who took a long and successful detour by way of medicine to literature. During his two-year post doctoral studies in Louisville, Kentucky and at University College in London, Bitó immersed himself in neurology and ophthalmology before receiving a position as researcher at the Department of Ophthalmology at Columbia University. Bitó claims it was in fact his love of literature and writing that directed his medical interest toward that of the brain and eyes. It was very early in his research career that he became aware of his interest in prostaglandins and their role in regulating pressure in the eye.

Bitó hypothesized that prostaglandins could contribute to reduced pressure in the eye, thus making them essential in treating glaucoma, which is characterized by increased intraocular pressure. His hypothesis was controversial and Bitó readily faced harsh scrutiny at conferences and symposia despite his sound convictions. On the contrary, leading researchers were largely convinced of prostaglandins’ contribution to increased pressure of the eye, as demonstrated in animal trials performed on rabbits. Bitó did not deny the results themselves referred to by so many, but instead pointed to the fact that the animals tested had received nearly toxic doses of prostaglandins. It was the dosage itself that likely lead to such different conclusions about the effects of prostaglandins. Another explanation was the fact that different types of animals responded differently to prostaglandins depending on their anatomy and the functionality of their eyes. Underdogs of the animal kingdom, such as rabbits, require the ability to scan their surroundings constantly. To this end, their eyes protrude, giving them a panoramic view. On the other hand, predatory animals such as cats and monkeys require sharp eyesight and the ability to focus. As a result, they are equipped with well protected eyes that sit deeper in the head.

To confirm this point in his reasoning, Bitó tested his hypothesis first on his own cat and later on monkeys that his colleague Endre Balazs had used for testing hyaluronic acid for Pharmacia. Bitó was pleased with the results as his theory seemed to have been proven. Certainly humans would respond to prostaglandins as had other predators. The first human put to Bitó’s test was he himself. Once again his theory was proven as he measured a decrease of pressure, even if redness and irritation were also experienced. Though it was apparent that the synthetic analogs used by Bitó were not optimal for use in the human eye, he was convinced that future development in the hands of pharmaceutical experts would resolve such related concerns. By this stage, Bitó had no aspirations about being involved in commercializing his discovery.
Bitó, he was largely uninterested or unaware of any possibility to earn money on his results either.

As Bitó was performing the administrative task of reapplying for his yearly research grant with the National Institutes of Health, he made a small but important discovery. Despite having filled out the same application in previous years, he had never noticed the question before. It was a box to be marked if earlier grants from the National Institutes of Health had led to clinically or commercially valuable results. Given the potential future of his earlier research, he affirmed the question on the application by checking a box and thought no more of it. A few months later, Bitó was contacted by the newly created Office of Science and Technology Development at Columbia University (OSTD). The office itself and the question on the grant application were directly linked, the result of a newly signed law by the Reagan administration in July of 1981. The new legislation was named The Bayh-Dole Act. It gave American universities strengthened legal standing with regard to ownership and control of potentially successful commercial ventures resulting from federally funded research. Commercial developments of such research were to be offered first to American companies.

László Bitó was informed by an OSTD representative that it was high time to begin the process of patent applications for his results within the framework of the prostaglandin project. Bitó’s knowledge of patents at the time was limited to what he had learned regarding the patent process experienced by Thomas Edison. He was unaware of the possibility of applying for patents on the basis of research: ”In biology, the only patent holder I could imagine was the Creator himself”, said Bitó.

Bitó’s patent application was submitted to the U.S. Patent and Trademark Office. In addition, OSTD agreed to begin actively searching for an American licensee. A contract was signed by Bitó and OSTD, stipulating that OSTD would complete the search within one year. As mentioned in Chapter 17, OSTD was unsuccessful in locating a willing licensee among the American companies that were approached. According to Bitó, OSTD’s results were based on two factors. First, there was a general skepticism toward a university’s ability to manage patents. Secondly, there was doubt within the prostaglandin community with regard to prostaglandins’ feasibility in treating eye illnesses at all. Likely, this doubt had become strengthened by the earlier tests performed on rabbits.

Bitó recalled a specific incident in 1977 or 1978 in which he had been invited to speak at the Annual North America Glaucomatologist Learning Ensemble. Bitó had taken it upon himself to invite one of the foremost experts on prostaglandin research in the hope that he had been convinced by Bitó’s work. Bitó could not have been more wrong. The expert he had invited was scathing in his public criticism of Bitó’s results at the
conference. A friend of László Bitó who attended the conference exclaimed: “That’s it!”

Bitó explains:

“I am certain that this was the main reason why, in spite of our many studies to discredit the very negative rabbit literature, no US pharmaceutical company was interested in developing a prostaglandin-based ocular hypotensive drug under license from Columbia University.”

Pharmacia was approached with regard to a possible license for László Bitó’s research when American options had been exhausted. Pharmacia would agree, but only after having first addressed its reluctance. Both Bitó himself and his research were carefully examined by Pharmacia. Among other things, Pharmacia contacted Anders Bill, professor of physiology at Uppsala University. Anders Bill characterized Bitó’s project as “next to ridiculous”, giving it a five percent chance of success, according to Bitó. Yet another person questioned in regard to the venture was Ernst Bárány, professor emeritus of pharmacology at Uppsala University. Bárány reportedly said: ”Bitó always has crazy ideas, but he was always proven to be right: go ahead and do it!”

Two decades of difficulties with intermittent glimmers of light

László Bitó was sadly mistaken in his belief that he would enter a quiet life of research now that a commercial home was found for his prostaglandin project. His largest concern early on was that nothing seemed to happen. He had periodic contact with project manager Helen Backlund and through her also Bengt Ågerup, despite Ågerup’s departure from Pharmacia Ophthalmics. He also began collaborating with Bahram Resul, the only researcher at Pharmacia working full time with the prostaglandin project initially. Their efforts centered on Resul producing new prostaglandin preparations that Bitó later tested in his lab at Columbia University. Their goal was to find prostaglandins that caused fewer side effects than those already derived. In his acceptance speech for having been awarded the Proctor Medal in 2004, Bitó mentioned his work with Resul: ”Bahram and I were very optimistic that we would find a PG derivative with reduced local side effects, but support for this project within Pharmacia started to dwindle.”

Sometime during the latter half of 1985, Bitó felt forced to take action. He contacted OSTD and asked for assistance. This led to the aforementioned letter from OSTD chief Jack Granowitz, who threatened to have the project removed from Pharmacia if activity levels did not increase. Indeed, a sense of urgency was awakened within Pharmacia after the correspondence from Granowitz. Whether this was a result of the letter itself,
or Johan Stjernschantz taking over the prostaglandin project in January, 1986 is unclear. Bitó’s opinion is likely best summarized by a note from his Proctor Medal speech: "The Savior Arrives and Sets his Sights Very High."

Stjernschantz’ injection of life into the project would later produce a blockbuster product. Despite this, László Bitó’s sentiment with regard to the two decades after Pharmacia’s initial involvement cannot be described as anything but painful. There were three main components of Bitó’s angst during the period:

- Events that threatened the project’s existence
- Attacks on the patent
- Attacks on the patent author, at times combined with attacks on Bitó personally

**Events that threatened the project’s existence**

In an unpublished manuscript from 2010, László Bitó describes the first such incident as having: “knocked the wind out of me”. Sometime during the winter of 1990/1991, he received a call from project manager Johan Stjernschantz. Stjernschantz explained that the iris of one of the test monkeys had turned brown during a toxicology test.

“Brown! What else, but melanin! Johan did not articulate the Melanoma word when he called me, and he did not have to utter it. The thought of it was enough to constrict my chest painfully and knock the air out of me. I told Johan that I will be in Uppsala in the morning.”

Closer examination would eventually alleviate the fears caused by the discovery. It was decided that prostaglandins were incapable of causing cancer in the eye. The discoloration was caused by other factors and was harmless. The project continued.

Bitó explains his initial dismay at the resulting changes in pigmentation in light of the difficulty of even finding a licensee for the project itself.

"If Pharmacia, the only company that was willing to give it a shot when Columbia and I were looking for a developer in ’83, would have dropped this project because of this pigmentation effect, no other pharmaceutical company would have touched it."

The next instance in which, as Bitó described it: “... my heart stopped and I thought I was going to die before it restarted with a big bang,” took place during an FDA hearing.

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27 László Bitó: "From blood aqueous barrier breakdown to the development of Xalatan, and a new approach to glaucoma management. The story behind the story.” Unpublished manuscript (2010)
in December, 1995. By this point, it was well understood that Xalatan could indeed cause discoloration in certain eye types. It was also known that the discoloration itself was harmless and ceased upon ending treatment with Xalatan. This fact seemed hardly relevant when a hearing committee member exclaimed: “... the discoloration could pose a major public health hazard for glaucoma patients.” Bitó felt there was no chance of Xalatan receiving approval: “… and I feared that what I worked for in much of my time for almost 30 years and devoted to almost totally the last five of them, would go down the drain.”

Bitó’s fears proved to be unfounded. Nearly half a year later, Xalatan was approved as a second-line treatment. Despite not achieving immediate first-line treatment status, a successful market establishment would occur. The approval itself was of little immediate comfort to Bitó, who carried with him a fear of repercussions caused by the discoloration outcry for years to come. It was not that Bitó or his fellow researchers doubted their own confidently presented conclusions regarding cancer risk. But rather, in the event that a glaucoma patient developed cancer in the treated eye, Xalatan would possibly be drawn in, even if the cancer itself was unrelated to Xalatan. Statistically speaking, this was a real possibility. Fortunately for Bitó, the odds were with him and no such scenario ever arose.

**Attacks on the patent**

László Bitó’s initial knowledge of patents was limited at best. By the time Xalatan was released, he had a much larger grasp of the patent process both legally and commercially. As a result of his better understanding, Bitó was fully capable of realizing the magnitude of seriousness in light of two competitors’ release of seemingly identical products. Essentially, they were Xalatan copies. The first was a product named Lumigan, introduced by Allergan and based on a prostaglandin called bimatoprost. The second was Travatan, sold by Alcon and based on a protaglandin called travoprost.

In both of these conflicts, legal processes were initiated. In the Lumigan case, Pharmacia Corp. was acting as defendant since Allergan tried to invalidate the latanoprost patent, and in the Travatan case Pharmacia was acting as plaintiff, since they sued Alcon for patent infringement. Both cases were settled during 2002 with the result that Allergan and Alcon were allowed to continue selling their products against paying a royalty to Pharmacia Corp. on realized and future sales. Allergan also had to
pay a lump sum of 120 mUS$. Whether a lump sum was paid also by Alcon is not known.\textsuperscript{28}

In 2004, Pfizer succeeded in halting plans by Par Pharmaceutical to introduce a latanaprost copy onto the market. This commercial victory was won after yet another legal process was initiated.

For László Bitó, the legal difficulties described above, as well as a number of similar incidents, resulted in an unexpected amount of work and worry not directly associated with research. Even Bitó’s original patent was subject to debate on different occasions, forcing Bitó to devote large amounts of time and energy in preparing legal testimonies.

\textit{Attacks on intellectual property}

Perhaps the most emotionally demanding aspect of the Xalatan project for László Bitó was the attacks questioning his sole ownership of the original patent. One such example was the so-called Stern case, which ended favorably for Bitó and will be returned to below. The most dramatic attack on Bitó’s intellectual property was never subjected to legal examination, however. The episode in question involved László Bitó’s closest partner during many years, Carl Camras. Camras would eventually shake Bitó to the core by demanding co-inventorship at a very late stage in the Xalatan process.

Bitó had grown accustomed to claims of partial ownership with regard to patent ‘353 when Camras’ demands were presented in October 2004. Throughout the course of Xaltan’s market prosperity, nearly a dozen former colleagues had informed either Columbia University or Bitó himself of contributions directly leading to the creation of Xalatan. Such assertions, when directed at Bitó personally, often began with “Certainly you remember when we discussed…” or, “Remember that time I advised you to…”. None of the cases led to legal action. It was therefore of great disturbance to Bitó when he learned that Columbia University was being sued by a former student in 2005. Not only was the former student suing for lost royalties, but also for the right to royalties on future sales.

\textit{The Stern Case}

Fredric Stern was a doctoral student who was given a semester long internship in László Bitó’s laboratory during 1980. Stern was involved in comparing studies of prostaglandins in cats and rhesus monkeys. Stern and Bitó presented the results of which in a jointly authored report. Stern claimed that it was he who had thought of

\textsuperscript{28} Source: Swedish newspaper \textit{Svenska Dagbladet}, October 29, 2002
using rhesus monkeys. The monkey proved later to be of large importance in showing prostaglandins pressure reducing properties. The fact that the report itself was an important reference in Bitó’s patent application further strengthened Stern’s confidence in demanding compensation. An additional point of relevance with regard to Stern’s claim was that he in fact was listed as first author of the report.

The latter of Stern’s allegations was easily defended by Bitó, as he had often allowed younger assisting researchers to stand as first author on reports in an attempt to boost their careers. Stern’s other arguments were dismissed as well and his demand for co-ownership was denied by the United States Court of Federal Appeals for the Federal Circuit. The court stated:

“Stern did not have an understanding of the claimed invention, did not discover that prostaglandins have an effect on IOP, did not discover that repetitive application of prostaglandins to the eyes of primates can maintain reduced IOP, and did not conceive of the idea of the use of prostaglandins to reduce IOP in primates. Furthermore, there was no collaboration between Stern and Bitó in developing a glaucoma treatment. Stern simply carried out an experiment previously done by Bitó on different animals, animals that Bitó had already determined would be good models for prostaglandins research. Stern's contribution is insufficient to support a claim of co-inventorship.”

Stern’s lawyers relentlessly pursued every judicial option available, making it a very expensive ordeal for the losing side. Bitó recalls Stern even proposing a settlement, which was immediately rejected by Bitó. A settlement would have likely encouraged others who had worked on the project to perhaps make the same attempt. According to Bitó, there were others who had contributed substantially more than Stern.

**The Camras Case**

Carl Camras (1953-2009) was a prominent researcher within ophthalmology who had worked as an assistant from 1976-1979 under László Bitó. He would later go on to work at the UCLA School of Medicine and Mt. Sinai School of Medicine. From 1991, until his death in 2009, he worked at the Department of Ophthalmology at the University of Nebraska Medical Center.

Camras was very much involved in the prostaglandin project, both in the original patent application as well as the subsequent joint venture between Columbia University and Pharmacia. Camras was entrusted responsibility of the phase 3 trials that preceded FDA approval of Xalatan in June 1996. In addition, Bitó claims that Camras’

contributions at FDA hearing a year prior were invaluable. When Bitó returned permanently to Budapest toward the end of the 1990’s, Camras confidently assumed his role as global ambassador, attending symposia and conferences in order to market Xalatan, as Bitó had for many years. So meaningful was Camras to the project, it was said that Bitó instructed Columbia University to direct a portion of his own royalties to him.

Before Carl Camras arrived at Columbia University in 1976, he had spent a year as a postgraduate student at Yale University. Like Bitó, Camras developed an early interest in prostaglandins. He authored a report in which he even speculated as to their possible pressure reducing properties in treating glaucoma. Though his supervisor would not allow the report to be published, Camras would later author many articles on prostaglandin use in treating glaucoma, a dozen of which were co-authored by Bitó.

László Bitó describes his relationship with Carl Camras as very good, both professionally and personally. These sentiments are not refuted by Camras. Bitó was therefore rather surprised when Carl Camras was described in a 2003 article as “primary inventor” with regard to patent ‘353. The article was based on an interview with the institute president at the University of Nebraska. Bitó chose to assume that the exaggerated claim was a purposeful attempt at receiving additional funding.

However, in the autumn of 2004, Bitó became aware that Carl Camras felt overlooked in terms of patent ‘353. Bitó then received a seven page letter from Camras, sent in the form of an e-mail. Among that which Camras wished to shed light on was his 1975 unpublished manuscript in which he hypothesized the usefulness of prostaglandins in treating glaucoma. The letter ended: “… please, let me know within 30 days of the date of this e-mail whether you will correct the error that has persisted for so long, and finally have me listed as a co-inventor on the patent. As stated above, if this does not occur, I am prepared to take additional steps to correct this injustice.”

Bitó had several reasons not recognize the validity of the claims put forth by Camras. Bitó’s main concern was avoiding a chain reaction of similar allegations by others previously involved in the prostaglandin project. Bitó himself is to have encouraged Camras to present his case in front of a judge. As reluctant as Bitó was in the face of yet more legal proceedings, he knew that this would be the best way to resolve the conflict. As Bitó’s attorney put it: “… just as every drug has side effects, we must regard such lawsuits to be the unpleasant side effect of successful inventions.”

The subject of co-inventorship was touched upon during a meeting I had in September 2013 with Orin Herskowitz, executive director of Columbia Technology Ventures, earlier called OSTD. Herskowitz claimed that conflicts of similar nature have never occurred during the hundreds of ventures supported by Columbia University that did
not realize commercial success. However, in every single project that obtained financial prosperity, there have been disputes of co-inventorship.

Bitó believes, or at least hopes, that the letter from Camras in 2004 was not founded on the basis of inner conviction, but rather at the advice of a legal counsel. That Camras never again escalated the conflict speaks to the latter. Furthering this belief are Camras’ own words in an article published in November, 2006 in Glaucoma Today. When asked: ”How would you describe your interactions with László Bitó, PhD, in the proof of concept for the prostaglandin-induced lowering of intraocular pressure,” Camras had a lengthy reply:

"I closely collaborated with Dr. Bitó from 1976, when I was a first-year medical student working in his laboratory, until 2001, when he retired from his scientific career. He is the person who is most responsible for developing prostaglandin analogs to the point of clinical usage. Without question, our patients would not be benefiting from latanoprost today if it were not for his innumerable, invaluable contributions. He clearly was the overall leader of this project. ….. I feel that few people, if anyone, could have taken this project to fruition as successfully as Dr. Bitó did. Because of his seminal contributions, millions of patients throughout the world are benefiting from the most successful class of medications in ophthalmology.

Dr. Bitó was generous in his support of me on a personal level and in my academic career. Without him, I could not possibly have accomplished all that I have, or attained the academic positions that I hold. I will value his tremendous influence on my personal life as a close friend, mentor, collaborator, colleague, and confidant forever.”

No ill will was directed toward Bitó and nothing was said of co-inventorship.

The story of Carl Camras seemed to be over regarding the dispute with László Bitó, if not for a November 2012 article in Archives of Ophthalmology. The article was entitled “Carl B. Camras, MD. Reflections on His Contributions to Glaucoma Research and Clinical Practice.” The author was Nancy L. Camras, Carl Camras’ wife of thirty years. The background of the article was, according to the author of the article, Carl’s dying wish to be remembered as: “… the first to hypothesize that prostaglandins lower intraocular pressure and had potential as a medication to treat glaucoma.” Recapping her late husband’s scientific career, his contributions to glaucoma research and his role in developing latanoprost, Nancy Camras concluded the article by describing ”the error of omission that prevented his recognition as its inventor.”

The professional relationship between Camras and Bitó is described in part according to the following: ”Although Carl had collaborated with Dr Bitó during medical school and throughout his physician training and later became a consultant for Pharmacia, Inc., he was not named as co-inventor on the latanoprost patent.”
The article also referenced statements by two of Carl Camras’ supervisors at Yale University 1974-1975. When asked: “Was it Carl’s idea that PG’s reduced IOP?” both replied: “Yes.” Dr. Ted W. Reid was quoted as saying: “Carl was the driving force for the whole idea of using PG for glaucoma. His ideas, his innovation and perseverance made this project work. László contributed to this project, but for him to get all the credit and none for Carl was a true tragedy and a gross mistake.”

The campaign waged by Nancy Camras was understandable and certainly not unusual. The unique aspect of her efforts was the fact that they were distributed in a scientific publication. Notably, a rather important factual mistake did not catch the eye of the article editor. When Nancy Camras described Carl Camras as co-inventor of latanoprost, she likely meant Bitó’s original patent, patent ‘353. Latanoprost was in fact the result of further development of Bitó’s patent, though neither Bitó nor Camras were central in its creation. Instead, it was Pharmacia & Upjohn scientists Johan Stjernschantz and Bahram Resul who were given credit for latanoprost, and who are referred to as the inventors on the latanoprost patent document.

**Bitó’s literary dream is realized**

In 1996, László Bitó was living as would be expected of a senior researcher at a premier university in the United States. Some two years later, he found himself on the verge of economic freedom as a result of Xalatan based royalties. Bitó realized that if he were ever to seriously entertain his dream of writing literature, the hour had come. It was a dream that had laid dormant since fleeing Hungary in 1956. There was but one last setback stemming from the detour that had become his scientific career. Bitó had assumed responsibility of representing Pharmacia & Upjohn in marketing Xalatan at numerous conferences and congresses, further influencing opinion leaders within the business of glaucoma treatment. Unbeknownst were the future legal processes, which would also devour much of his time and energy. The solution to his commercial commitments was Carl Camras, who agreed to take over Bitó’s role. Not wasting any time, Bitó resigned from Columbia University in 1997 and was awarded the title “Professor Emeritus in Ocular Physiology, and Special Lecturer.” He then moved back to Budapest in order to devote himself to writing.

László Bitó had not been entirely inactive in his writing during his years as a researcher. He published two books in 1994 and 1996 respectively. Both books deal with modern Hungarian history, based on Bitó’s own impressions and memories, and are only available in Hungarian. Bitó’s literary breakthrough came with his 1998 work, “Abraham and Isaac.” Translated into a number of languages, the book was even performed as a play at one of Budapest’s most respected theaters. “Abraham and Isaac”
as well as Bitó’s latest publication, “Gospel of Anonymous,” can best be described as counter conditional accounts of biblical narratives. Bitó is also an active commentator on Hungarian politics, often expressing strong criticism of the current government (March, 2015). In addition, he is actively involved in the debate surrounding euthanasia. His book published on the subject is called: "Eutélia – Euthanasia” (Blissful Life – Peaceful Death). Eutélia is a concept created by Bitó himself, as an alternative to euthanasia.

As I met with László Bitó during the course of two summer days in 2013, I concluded by asking a question he had likely fielded many times before: ”Why would you leave Columbia University at the peak of your career?” To this, Bitó responded: ”I had done everything I could to forestall physical blindness. And I consider myself fortunate, that after that I got a chance to stand up against spiritual blindness through my essays, short stories and especially my novels of Biblical reinterpretations that try to overcome the tunnel vision of the last couple of millennia.”

The extent of Bitó’s financial prosperity is unknown. Columbia University discloses no information regarding individual contracts, Bitó says he is unsure himself, and no detailed information has come forth from either Pharmacia or Pfizer. According to information presented in Chapter 18 above, his royalty revenues likely range from 80 to 132 mUS$. Part of László Bitó’s income has been used to start the The László Bitó and Olivia Cariño Foundation. As part of a joint effort, Bitó and his wife began the venture in order to benefit cultural projects, mostly musical. The Foundation donated some 9.2 million US$ to The Bard College Conservatory of Music for the construction of the László Z. Bitó ’60 Conservatory Building. Commenced in 2013, the donation was likely the largest in the foundation’s history.

The Bitós’ foundation also sends talented Hungarian youths to study at Bard College and Juilliard School in New York. In addition to the donation to Bard Colleges Conservatory of Music, a 1.7 million US$ contribution was given to the Bard College undergraduate program. Bitó presented the contribution with the following message: ”It is my pleasure to support the budding conservatory program of Bard, remembering the support I received from the college that started my academic career.”
"Welcome to the place where the world’s first hyaluronic filler was invented.” So read the greeting on the wall when I visited Q-Med, a Galderma Division in Uppsala, Sweden, in March, 2014. It is a message not entirely at peace with the truth. For start, the NASHA-patent and its first resulting product, Restylane, was invented elsewhere in Uppsala. Perhaps this is but a minor detail. More importantly, however, is the fact that the world’s first hyaluronic filler was not in fact Restylane, but rather Hylaform. This part of the book aims to explain the relationship between the two products and their impact on a new product area within the cosmetics market.
CHAPTER 21: New products emerge from the quest for eternal youth

More and more people around the world are trying to rejuvenate their facial appearance through the use of products such as Botox® Cosmetic, Juvéderm® and Restylane®. At the brink of this global movement is Allergan, the world leader in facial injectables. In 2013 alone, the facial aesthetics market was worth some 2.5 billion US$, a figure expected to more than double by 2020 (GBI Research).

On November 17, 2014 it was announced that the pharmaceutical company Actavis plc and Allergan Inc. had entered into a definite agreement under which Actavis will acquire Allergan for 66 billion US$30. This is can be compared with the 60 billion US$ Pfizer paid for Pharmacia Corp. in 2003, or the 119 billion US$ Pfizer was prepared to pay for AstraZeneca in May, 2014. Actavis started its operations as late as 1983 in Illinois, USA, but has since 2013 its global headquarters in Dublin, Ireland. Actavis’ acquisition of Allergan was preceded by a serious attempt by the Canadian company Valeant to gain control over Allergan through a so-called hostile takeover.

Allergan’s leading position on the facial aesthetics market was made possible by their successes with Botox Cosmetic, a so-called neuromodulator, and Juvéderm, a dermal filler. By combining the two substances – for example Botox for the upper half of the face, and Juvéderm for the lower half, an effective wrinkle reducing result is said to be achieved. The active ingredient in Botox Cosmetic is a potent poison, Clostridium botulinum, which acts as a muscle relaxing agent. According to the Swedish periodical Illustrerad Vetenskap (2013-02-20), Clostridium botulinum is so poisonous that a mere 500 grams of the substance would be enough to kill the entire population of the world.

The original purpose of Botox was for treating neuromuscular disorders, such as strabismus, spasms and migraines. Its wrinkle reducing properties were discovered by mere chance in 1987 by doctors Jean and Alastair Carruthers. The presence of Botox grew strong during the 1990’s for use in plastic surgery. In 2002, Allergan was awarded FDA approval for a less concentrated version of the same product, Botox Cosmetic, for use in cosmetic facial treatment.

Prior to the introduction of Botox, collagen was the most commonly injected substance for reducing wrinkles and age lines. In 1995, Biomatrix successfully received CE certification for Hylaform, making it the first hyaluronic acid-based filler on the cosmetics market. Just a year later, Q-Med was awarded the same certification for its

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30 Reuters, November 17, 2014
product Restylane, essentially spelling the beginning of the end for collagen as the most important dermal filler.

According to Allergan’s annual report from 2013, sales of Botox Cosmetic were 912 mUS$. Facial aesthetics product net sales, Botox Cosmetic not included, were 478 mUS$, as compared to 388 mUS$ the year before. The dominating brand among Allergan’s facial aesthetics products is Juvéderm, a product originally developed by the French company Corneal, which was acquired by Allergan in 2006. More on this will follow below. In 2011 Allergan presented Juvéderm as “the world’s No.1 selling dermal filler brand”.

Main challengers to Allergan on the U.S. as well as the global market are the Swiss company Galderma, the Canadian company Valeant, and the German company Merz. Galderma acquired the Swedish company Q-Med in 2011. Valeant acquired Q-Med’s licensee on the U.S. market, Medicis Pharmaceutical Corp., in 2012 and has during 2014, as mentioned above, made an unsuccessful attempt to take over Allergan. Merz acquired its Swiss licensor Anteis in 2013.

Like Allergan, the three main competitors also offer customers a package deal. It contains a botulinum for the upper parts of the face and a hyaluronic acid-based dermal filler primarily for the lower part of the face.

In Galderma’s case, the most important botulinum is a product named Dysport, sold in Europe as Azzalure. The product is sold under license from the French company Ipsen. The most notable dermal filler is Restylane, which on the U.S. market is complemented by Perlane, a more highly cross-linked version of Restylane. Previously, a company called Medicis Pharmaceutical Corp. had sales rights for Restylane, Perlane, and Dysport for the American market. But as the result of an agreement between Medicis owner Valeant in 2014, Galderma has reclaimed American sales rights for these products.

Canadian Valeant became involved in the facial aesthetics market in 2011 after having purchased Dermik, a division of Sanofi that sold dermatology products in the U.S. and Canada. Among Dermik’s product portfolio is Sculptra, one of the few remaining collagen based dermal fillers on the market. With Valeant’s purchase of Medicis Pharmaceutical Corp. in 2012 came control over American sales rights for Q-Med developed Restylane and Perlane. As mentioned, these sales rights were later re-sold to Q-Med’s new owner Galderma at the start of 2014. This was a strategic move from Valeant’s side in their attempt to acquire market leader Allergan which, as has been mentioned above, failed.

Principal product of German Merz is the dermal filler Belotero® Balance, previously sold in the U.S. and a handful of European countries on license from Swiss Anteis. As
part of Merz’s advance on the market, the company purchased global sales rights for French Pierre Fabres’ hyaluronic acid-based products under the brand Glytone®. This was followed by an outright acquisition of Antéis in November 2013. The botulinum of Merz is named Xeomin®, which received FDA approval in July 2011. The product is marketed under the brand Bocouture® in Europe.

Merz’s planned advance on the American market was temporarily stalled in March 2012 as a local court issued a ten-month sales ban on Xeomin as the result of unethical behavior. Merz was accused of improperly obtaining business secrets and other confidential information by recruiting sales people from Botox manufacturer Allergan.

Other examples of hyaluronic acid-based dermal fillers are Teosyal® (Swiss Teoxane), Stylage® (French Laboratoires Vivacy), Prevelle® Silk and Puragen® (manufactured by Genzyme and sold by Mentor), and Dermavisc® and Decoria® (Swedish Bohus BioTech). Aside from all being dermal fillers, the common denominator among almost all of these products is their origin in Healon. How such a spread of information between the different companies was made possible will be explained below.
CHAPTER 22: The discovery of hyaluronic acid’s potential within the beauty industry

Hyaluronic acid’s potential within the beauty industry can be said to have come about due to a misconception regarding cabbage.

The incident began as the result of Marianne Balazs (Endre’s daughter) having read an article in Vogue magazine in the spring of 1974. In it, Vogue claimed that the beautiful completion often seen in Russian women could be attributed to their large consumption of cabbage. Cabbage was said to contain large quantities of hyaluronic acid according to the article. The author of the piece was French beauty guru Aida Grey, who owned salons in Beverly Hills, New York and Paris. In order to receive the same advantages seen in Russian women, Aida Grey had been promoting cabbage juice and cabbage tablets among her clients.

Marianne showed the article to her father, who could not believe his eyes. How could anyone claim that there was hyaluronic acid to be extracted in cabbage? Hyaluronic acid is not present in any plant known to man. At this point, Endre Balazs was determined to put a stop to the spreading of such nonsense. He contacted Aida Grey. Balazs, who lived in Boston at the time, arranged a meeting with Grey in New York at the Plaza Hotel. While waiting in the hotel lobby, he was not alone. Balazs began chatting with a 70 something year old women who also happened to be waiting for Aida Grey. The woman with which Balazs found temporary company was fellow Hungarian legendary beauty icon Ella Baché. As it turns out, Baché was one of Grey’s most important suppliers of beauty products, a line of which she was personally responsible. She was also the owner of a number of high end beauty salons.

Balazs soon found himself in the midst of both producer and marketer of the cabbage farce. Apparently, Balazs managed to hold his criticisms to a considerable level of diplomacy. Balazs quickly moved on from the cabbage discussion in order to explain the benefits of hyaluronic acid’s moisture retaining properties. These properties were of course of great interest to his hearers. By the end of the encounter, Balazs had agreed to produce a type of hyaluronic acid according to unique specifications. Baché would be in charge of production, and Aida Grey would market and sell the end result.

After much trial and error a preparation was produced which could be further refined to Aida Grey’s demands. The work in developing the new raw material was performed by Balazs’ wife, Janet Denlinger in close collaboration with her colleague at The Eye Institute of Columbia University, Betty Morales, who later would become Biomatrix’ first paid employee. Though no one involved initially understood what magnitude the work would have in terms of a final product, the result proved to be significant.
Eventually, a patent application was submitted for the means of manufacturing the special type of hyaluronic acid. The resulting product was named Biomatrix®, the same name given to the company that Balazs and Denlinger had formed.

The outcome of their efforts was launched in 1981 in Ella Baché’s salon in Paris. Lurogel® and Elastogel® were introduced as the world’s very first skin care products containing hyaluronic acid. Later that same year, Aida Grey launched Dermabien®, yet another skin care product containing Biomatrix.

As mentioned in Part III, one of the most important driving forces behind the 1981 creation of Biomatrix was frustration on the part of Endre Balazs in terms of Pharmacia’s lack of interest in hyaluronic acid for treating joint disorders. In joining forces with Aida Grey and Ella Baché, Balazs had found a valuable source of funding in order to develop his plan of creating a finished product for treating joints.

In a search to further expand this source of financial security, Biomatrix contacted several large cosmetics companies in an effort to spark further interest in hyaluronic acid’s beneficial properties within the industry. The outcome was an agreement in 1982 with Estée Lauder. The partnership proved to be a huge success as Estée Lauder produced an immediate top selling product, Night Repair®. Even today, Night Repair is one of Estée Lauder’s best selling products. As long as Balazs and Denlinger remained majority owners of Biomatrix, until the year 2000, Biomatrix was the main supplier of hyaluronic acid for Night Repair.

**Hylaform – the first hyaluronic acid-based dermal filler**

Following their rise of success within the skin care market, Biomatrix opted to increase the breadth of its focus, which was “viscosupplementation”, to also include “viscoaugmentation.” These concepts were likely coined after the term “viscosurgery”, invented by Endre Balazs to denote Healon applications for eye treatment.

Specifically, the concept of viscoaugmentation involved injecting hyaluronic acid under the skin in order to eliminate or decrease wrinkles. The method itself already existed, but utilized another substance called collagen. Use of collagen for such applications was subject to a number of side effects, primarily allergic reactions. Demand for a collagen substitute for wrinkle reduction steadily grew and in releasing hylan B in 1984, Balazs had succeeded in crosslinking hyaluronic acid in order to form a gel.

Toward the end of 1984, Bengt Ågerup made his inception in Biomatrix. Initially working part time as a consultant, Ågerup was in 1987 inaugurated as CEO for
Biomatrix’ Swedish affiliate in Uppsala. One of Ågerup’s first assignments was to begin clinical trials on hylan B, Balazs’ hyaluronic acid in gel form. As trials began in West Germany, focus was initially centered on using hylan B in conjunction with reconstructive breast surgery. However, this focus was eventually shifted toward hylan B’s properties of viscoaugmentation, or filling. The cosmetic application of this property involved reducing wrinkles and smoothing over scars. In 1990, multicenter trials were underway in Germany as well as in Sweden and the U.S., and the resulting product was named Hylaform®.

Hylaform received CE certification in November 1995, making sales within the European Economic Community possible and paving the way for approval in some 10 other countries before the end of the decade. In 1995, Biomatrix submitted an application for pre-market approval by the American FDA which was later withdrawn for unknown reasons. FDA approval was eventually secured in April 2004, four months after approval of Q-Med’s Restylane and four years after Biomatrix was sold to Genzyme.

Hylaform’s 1995 CE certification lead to Biomatrix signing a distribution agreement with Collagen Aesthetics Corporation the same year. At the time, Collagen Aesthetics were market leading with their collagen based dermal fillers Zyderm and Zyplast. The agreement resulted in Biomatrix receiving 5 mUS$ initially and royalties on future sales. In less than six years, three significant events would drastically change the direction of Hylaform’s future development. One of these events was the fact that Collagen Aesthetics Corporation was purchased by Inamed in 1999, world leader in silicone breast implants. Another was that Biomatrix itself was purchased by Genzyme in 2000. The third, and probably most important event, was that Q-Med AB, a company owned by the CEO of Biomatrix’ Swedish subsidiary, Bengt Ågerup, launched a competing product called Restylane.

**Dermal fillers gain a foothold on the facial aesthetics market**

At the onset of 2004, Inamed was in the process of extensively expanding its product line. To this end, they had acquired exclusive distribution rights for Juvéderm in North America and Australia as well as non-exclusive rights for some of Europe’s largest markets. Juvéderm, which was produced by the French company Corneal, was similar to Hylaform in that both are hyaluronic acid-based dermal fillers. However, they differ significantly in production technology. While Hylaform is produced using the comb of a rooster, Juvéderm is produced by way of bacterial fermentation. Once Inamed’s new distribution rights were obtained, they had a product line that spanned the full spectrum of dermal fillers, from collagen based Zyderm, Zyplast, CosmoDerm and CosmoPlast...
to rooster comb based Hylaform and bacterially fermented Juvéderm. In December 2004 Inamed extended its dermal filler family with yet another product based on bacterial fermentation, namely Captique, produced by Hylaform’s owner, Genzyme Corporation. It was by no accident that Inamed had managed to acquire seven different products with three different production methods.

The aggressive push by Inamed awakened the competition. In March of 2005, the U.S. company Medicis attempted to purchase Inamed for 2.85 billion US$. Having recently obtained licensing rights for the American market for the Swedish company Q-Med’s Restylane and Perlane, Medicis now wanted a stronghold on the market by also achieving access to Juvéderm, Hylaform, and Captique as well as Zyderm and Zyplast. Later that year, Medicis was outmaneuvered by Allergan, who offered to purchase Inamed for 3.3 billion US$. Allergan’s strategy was largely the same as Medicis. By complementing their product line, already armed with Botox Cosmetic, with dermal fillers, they would be able to lead the market in facial injectables. In addition, Restylane’s dominant position, defended by Q-Med on the European market, and by Medicis in the U.S., would be seriously threatened. Worth noting is that Restylane received FDA approval in December 2003, four months before Hylaform (April 2004) and two and a half years before Juvéderm (June 2006). Another reason for Allergan’s interest in Inamed, was that Inamed had acquired the distribution rights to a botulinum-based product developed by the French company Ipsen, which was sold on the European market under the brand name Dysport. The product was not yet approved by FDA, but was seen by Allergan as a big potential threat for Botox Cosmetic.
CHAPTER 23: The origin of Restylane and Juvéderm

As mentioned in Chapter 14, the partnership between Endre Balazs and Bengt Ågerup started shortly before Ågerup was forced from Pharmacia Ophthalmics at the end of 1984. In March of 1985, three months after Ågerup had signed the consultant agreement with Biomatrix, he started the Uppsala-based company Q-Med AB. The company was largely unproductive during its first years of existence and no notable activity took place until May of 1988. Q-Med’s aspirations would not be revealed until the release of its annual report for 1989/90. The report made clear that Q-Med’s aim was to contract manufacture pharmaceuticals on a small scale for clinical trials or short term purposes. Q-Med also announced that it had made two important business acquisitions during the same period. The outcome was a 50 % ownership of both Up Will Investor AB and Equinord KB.

The first mention of Q-Med during business correspondences between Ågerup and Biomatrix took place in the spring of 1989. Ågerup expressed Q-Med’s interest in utilizing hyaluronic acid by way of adhesion: ”... outside of applications already under development within or outside of Biomatrix.” Nothing became of Q-Med’s interest and it is not mentioned again during the subsequent three or four years.

Bengt Ågerup took over as CEO for Svenska Biomatrix in 1987. One of Ågerup’s most pressing tasks as CEO was organizing and carrying out clinical trials for Synvisc (osteoarthritis), Hylaform (wrinkle reduction), and Gelvisc Vet (joint disorders in horses). Ågerup’s first contacts with the cosmetics market were in other words made in his role as CEO of Svenska Biomatrix AB. As financial problems arose for Biomatrix in 1988/89, it became clear that external financing was needed in order to maintain and follow through with the clinical trials both planned and underway for Synvisc at the Swedish affiliate. The situation was resolved through the creation Up Will Investor KB, a company started on Ågerup’s initiative, who was able to secure a number of investors willing to pitch in 0.5-1 mSEK each, 7 mSEK in total (= 1.2 mUS$). Those who invested were assured repayment in the order of 6% of future sales of Synvisc from those markets for which clinical trials were intended. It would prove to be a most lucrative investment.

Bengt Ågerup was a central player in the affairs of Biomatrix from the end of 1984 well into the 1990’s. His assignment as CEO for Biomatrix’ Swedish affiliate lasted from 1987 to 1997. His work load at the affiliate varied between half time and full time, with the exception of his last two years with the company. After the clinical trials and subsequent CE certification for Synvisc and Hylaform in 1995, Ågerup’s work at Biomatrix decreased in magnitude. Despite Ågerup’s half- to full time assignment for
Biomatrix at the beginning of the 1990’s he had time also for other projects. In fact, he was diligently working on the following three enterprises of which Biomatrix and Balazs had little or no knowledge:

- Formation of the company Bohus BioTech in Strömstad, whose purpose was creating hyaluronic acid from rooster combs for use in hyaluronic acid-based pharmaceuticals and surgical devices for eye surgery. A competitor to Healon, and also a potential competitor to Synvisc, in other words.
- The dissemination of knowledge regarding manufacturing hyaluronic acid from rooster combs for the French company Corneal.
- Developing a hyaluronic acid-based dermal filler within Q-Med (Restylane) by way of bacterial fermentation.

**Bohus BioTech AB – a Pharmacia Ophthalmics spin-off and a challenger to Healon**

Bohus BioTech AB is a company located in Strömstad, a small town on the west coast of Sweden. Bohus BioTech produces hyaluronic acid-based products for ophthalmic, aesthetic and orthopedic treatments. The company has some 30 employees and reported revenues of approximately 9 mUS$ in 2013. Until recently, all of the company’s products were based on hyaluronic acid from rooster combs. In 2014, however, Bohus BioTech launched a dermal filler under the brand name Decoria, based on bacterially fermented hyaluronic acid.

The origins of Bohus BioTech can be traced back to a dialogue that started at the beginning of 1990 between Bengt Ågerup and a previous colleague at Pharmacia Ophthalmics, Daniel Ogbonnaya. When the talks began, Ogbonnaya, an expert on the production of rooster based hyaluronic acid, was still employed at Pharmacia Ophthalmics. Eventually, Göran Ågerup, Bengt Ågerup’s cousin and real estate businessman, and Hans Åkerblom, previous CEO of Pharmacia Ophthalmics, were also invited to participate in the discussions.

The discussions revolved around the possibility of starting a company specializing in the production and distribution of a rooster based hyaluronic acid for the cataract surgery market. In other words, a direct competitor to Healon. The company was to be located in Strömstad, where a new production unit was intended. Daniel Ogbonnaya was to become CEO of the company while Bengt Ågerup would be responsible for research and marketing operations. Göran Ågerup and Hans Åkerblom were asked to become funders of the project, an invitation they accepted by investing 1 mSEK each (approx. 0.15mUS$). Worth noting is the fact that both Göran Ågerup and Hans Åkerblom had, shortly before the start of Bohus BioTech, participated in the creation
of Up-Will Investor KB, the company established to enable continuation of the ongoing clinical trials for Synvisc in Europe (see Part III).

Shortly before operations at Bohus BioTech started in August 1992, Daniel Ogbonnaya resigned from his job at Pharmacia Ophthalmics. Knowledge quickly spread at Pharmacia Ophthalmics that Ogbonnaya was planning to create a competitor with the help of Bengt Ågerup and Hans Åkerblom, i.e. the former CSO and CEO of the company. The reaction was unfavorable and legal action was considered, according to a former company executive. The fact that Ogbonnaya’s signature was necessary on a recently submitted patent application for a new Healon composition is said to have been the main reason for no such action being taken.

Annual reports for 1992-94 show that Bohus BioTech was initially a subsidiary of Andersson & Ågerup AB in Uppsala, and from 1993 a subsidiary of Ågerup & Ågerup AB, both of which were controlled by Göran Ågerup. Fifty percent of the shares of Bohus BioTech were given to Bengt Ågerup as “sweat equity”. The remaining 50 percent was shared equally between Göran Ågerup and Hans Åkerblom. Between Bengt Ågerup and Daniel Ogbonnaya an agreement was in place stating that Ogbonnaya would receive half of Bengt Ågerup’s shares when certain milestones had been met.

Until Bohus BioTech had received the necessary approval for the manufacture and sale of medical devices, which was not until 1994, all business activities had to be channeled via companies owned by Bengt Ågerup, primarily Q-Med, that possessed the necessary approvals. The name of the hyaluronic acid-based product sold by Q-Med on behalf of Bohus BioTech on the international cataract market was Microvisc®. The trademark was registered by Q-Med in Sweden in March 1992, and in Canada in November of the same year. The Microvisc trademark was eventually acquired by Bohus BioTech.

The Canadian incident

Through Microvisc, Endre Balazs and his co-workers at Biomatrix became aware of that Bengt Ågerup was involved in the manufacturing of a product in direct competition with Healon on the cataract surgery market. The revelation was made in July 1993, when it became known that 14 patients at the Jewish General Hospital in Montreal had suffered eye infections after undergoing cataract surgery. An investigation revealed that the infections were caused by the ophthalmic viscoelastic device used in connection with the operations, Microvisc Plus, produced by the

31 The Pharmaletter (1993)
Swedish company Q-Med and sold by a Canadian subsidiary of the French company Domilens.

The Canadian incident was commented on in the 1993/94 annual report of Q-Med as follows: “A claim has been lodged against Q-Med due to impurities in a batch manufactured in 1993 and sold in Canada. The company’s liability insurance is expected to cover the claims.” In an email correspondence with me in October 2014, Bengt Ågerup claims that the side effects in Canada were caused by the hospital storing the products in a room exposed to sun. According to Ågerup, the damages, which amounted to approx. 1.5 mUS$, were shared equally between Q-Med’s insurance company and the hospital.

When Endre Balazs learned about the Canadian incident he insisted on being informed regarding the original source of the hyaluronic acid involved. In a letter to Balazs, Ågerup provides the following information: “… I am unable to disclose the source of the hyaluronan raw material but can assure you that it in no way originates from Biomatrix or its proprietary technology.”

A turbulent period in the aftermath of the Canadian incident

The development of Bohus BioTech proved more strenuous than Bengt Ågerup and Daniel Ogbonnaya had envisioned. Toward the end of 1993, the company was facing substantial economic difficulties due to insufficient liquidity. The state of the company required immediate action. One of the funders, Göran Ågerup, proposed that the four partners should inject the company with new capital by way of a new stock issue. According to Daniel Ogbonnaya and Göran Ågerup the proposal was dismissed by Bengt Ågerup, who instead thought the company should be liquidated.

The general uncertainty caused by the Canadian incident and the divergent views on how the liquidity crisis of the company should be solved led to Hans Åkerblom’s departure. In connection with this, he transferred his shares to Göran Ågerup, a transfer that took place without Bengt Ågerup’s knowledge, according to the latter.

The liquidity crisis of Bohus BioTech at the end of 1993 was resolved, at least temporarily, by Göran Ågerup lending the capital needed to complete all ongoing preparatory projects, including the construction of the new plant in Strömstad. The balance sheet of the 1993 annual report of Bohus BioTech shows an increase of long-term debt from 0.678 mSEK in 1992 to 4.183 mSEK (approx. 0.55 mUS$) at the end of 1993.
A misplaced letter causes conflict

The satisfaction after having solved the economic dilemma toward the end of 1993 was short-lived. In 1994, a new conflict arose among the three remaining founders of Bohus BioTech AB. The action was set off by a letter from the French company Corneal, addressed to Bengt Ågerup, which mistakenly ended up in his cousin Göran’s mailbox. According to Daniel Ogbonnaya and Göran Ågerup, the letter revealed that Bengt Ågerup was involved in teaching Corneal, a company specializing on the production of intraocular lenses, how to produce their own rooster comb-based hyaluronic acid. This was an assignment he had taken on as a private consultant. We will soon return to the details surrounding Ågerup’s cooperation with Corneal. According to Göran Ågerup and Daniel Ogbonnaya, Bengt Ågerup’s cooperation with Corneal, which would result in a new competitor on the cataract surgery market, was the main reason why they and Bengt Ågerup decided to go separate ways.

There is said to have existed a partnership agreement according to which disloyal behavior was punishable with a penalty of 5 mSEK. Daniel Ogbonnaya was prepared to take the case to court, while Göran Ågerup preferred to settle the dispute out of court, despite strongly disagreeing with his cousin’s behavior. One reason for this was for the sake of the rather uncommon surname the two shared. Yet another was that Göran Ågerup and Hans Åkerblom remained as partners with Bengt Ågerup in Up-Will Investors KB (see Part III). The settlement implied, according to Göran Ågerup, that Bengt Ågerup left his ownership in Bohus BioTech in exchange for revenues he had received from selling Microvisc on Bohus BioTech’s behalf, which were still kept by him.

Bengt Ågerup’s explanation as to why he left Bohus BioTech is linked to a series of events ignited by the Canadian incident mentioned above. According to Bengt Ågerup, the incident scared Hans Åkerblom so much that he sold his part to Göran Ågerup, without informing Bengt. He also claims that cousin Göran and Daniel Ogbonnaya began conspiring against him, something he connects to the fact that Göran had a summer house close to Strömstad. This led to an unsustainable situation, which was solved through a settlement which meant that Bengt Ågerup left Bohus BioTech. The settlement also included other agreements which, according to Bengt, were never fulfilled.

The reconstruction of Bohus BioTech

After both Bengt Ågerup and Hans Åkerblom having left Bohus BioTech AB, Daniel Ogbonnaya and Göran Ågerup entered into negotiations with German Merck KGaA. After deliberations that lead to new issue of stock and funds in 1995, Merck KGaA had obtained 50% ownership of Bohus BioTech AB. The remaining 50% was owned
equally between Göran Ågerup and Daniel Ogbonnaya. The partnership with Merck was brief. In March 1997, Swedish Medical Products Agency revoked Bohus BioTech AB’s sales license for Microvisc due to reported side effects. As a result, Bohus BioTech AB temporarily lost its CE certification two months later. The state of urgency became too much for Merck, which sold its 50% ownership to Daniel Ogbonnaya.

Despite seemingly insurmountable obstacles in the form of Bengt Ågerup and Hans Åkerblom exiting, prohibited sales for Microvisc, temporarily losing CE certification and Merck’s withdrawal, Bohus BioTech AB has succeeded. The company is now focused on exports, is profitable, has some 30 employees, and boasts a turnover of approximately 9 mUS$ (60 mSEK) in 2013. Bohus BioTech AB is active within all three traditional markets for hyaluronic acid: ophthalmology, osteoarthritis and wrinkle reduction. The company’s products covering the three markets, respectively, are, Microvisc, Lubravisc®, and Dermavisc®. The ophthalmology market has proven to be the most lucrative, though the cosmetic use of Dermavisc has increased steadily. The company has recently launched its first product based on bacterial fermentation, a dermal filler with the brand name Decoria®. The ownership of the company has remained unchanged since 1997. Even as Daniel Ogbonnaya has since resigned as CEO, his 75% ownership remains, as well as Göran Ågerup’s 25%.

**Corneal and Juvéderm – diffusion of knowledge that leads to new competition**

The French company Corneal was started in 1986 by the Polish born optician, Waldemar Kita. When Kita’s former employer, Revlon Vision Care, was purchased by Pilkington PLC, he saw an opportunity to start a company of his own, Corneal, specialized in the production of intraocular lenses. This was a market segment growing very rapidly thanks to the development of the cataract surgery market.

After a while Corneal realized an unforeseen obstacle in selling the intraocular lenses. A necessary component when implanting intraocular lenses is hyaluronic acid. For convenience, most eye physicians prefer to purchase intraocular lenses and hyaluronic acid as a package. Such “package solutions” were already being sold by Pharmacia, initially through a subcontractor producing intraocular lenses, and later by producing its own.

Corneal began searching for a suitable supplier of hyaluronic acid and finally found Bengt Ågerup based on a recommendation by Ilan Hoffman, a former Pharmacia employee who was heading the Canadian subsidiary of Domilens, a French producer of intraocular lenses involved in the “Canadian incident” mentioned above. Corneal’s representative in its dealings with Bengt Ågerup was Gilles Bos, who was a young nuclear physicist with a degree from one of the foremost engineering “Grande Ecoles”
in France. Originally employed within the French atomic weapons program, Bos was enticed to join Corneal in 1988. “We were in desperate need of hyaluronic acid” Bos recalls, when we meet in April 2014. “Before we found Bengt Ågerup we even bought Healon from Pharmacia’s Swiss subsidiary in Geneva. The syringes were smuggled to France in the trunk of my car, and were then given to the ophthalmologists, free of charge. That was the only way we could sell our IOL’s.”

After initially having bought hyaluronic acid under the Microvisc label from Bengt Ågerup, who, as far as Gilles Bos remembers, acted as a representative of Bohus BioTech, Ågerup one day offered to aid Corneal in producing its own hyaluronic acid by teaching them the production method. This happened toward the end of 1992. Corneal’s owner, Waldemar Kita, accepted the offer and Gilles Bos was assigned the task of receiving Ågerup and overseeing his involvement in the project.

Ågerup’s tutorship sent him to Corneal’s factory in Annecy, 40 km south of Geneva, two days a week every other week during almost two years, according to Gilles Bos. With Ågerup’s help, Bos and his colleagues learned to raise and slaughter roosters, extract hyaluronic acid from their combs, and how to homogenize and purify the hyaluronic acid. Initially, Corneal was in need of 1 kilogram of hyaluronic acid which was delivered by Bengt Ågerup. At Ågerup’s suggestion, Corneal attempted to start its own rooster farm, but their efforts did not result in self-sufficiency. When the project with Ågerup had concluded, Corneal started to purchase hyaluronic acid from Bohus BioTech AB as well as rooster combs from the Swedish company Västfarm AB in Färgelanda.

Late 1994 marked the end of the partnership between Ågerup and Corneal as Corneal received CE certification for its own hyaluronic acid. The immediate result of Ågerup’s knowledge transfer to Corneal was the emergence of another producer of rooster comb-based hyaluronic acid on the international market. Not only was Corneal able to sell hyaluronic acid under its own brand name, Viscorneal and Viscorneal Ortho. They also managed to become a supplier to the Japanese company Nidek, which sold the Corneal produced hyaluronic acid under the trademark Nidelon®, and to Allergan, which sold Corneal’s hyaluronic acid under the trademark Allervisc®. The deliveries to Allergan were of such magnitude that they accounted for almost 20 percent of Corneal’s total revenues at the end of the 1990’s. Ågerup had, in other words, actively participated in creating new competitors to Bohus BioTech AB as well as to Pharmacia (Healon) and Biomatrix (Synvisc). But the most significant result of his knowledge transfer had not yet come to light, a result that would have a strong impact on his own future business. What I am referring to is Juvéderm, a product that will be returned to below.
During a meeting between Gilles Bos and Bengt Ågerup toward the end of the knowledge transfer project, Ågerup placed a glass bottle upon Bos’ desk. Ågerup then proceeded to explain that the bottle contained a new type of cross-linked hyaluronic acid produced by bacterial fermentation. Ågerup concluded by assuring Bos that he had no intention of revealing how it was produced, as their agreement had only encompassed rooster comb-based hyaluronic acid. Ågerup left the bottle on Bos’ desk where it remained as a source of inspiration for nearly a year. Alone in his office, Bos held the bottle up to a lamp in order to examine its contents. The only defining characteristic he could make out was a small number of tiny particles. Feeling challenged, he dedicated his work at Corneal to creating hyaluronic acid-based from bacterial fermentation, free from contaminating particles. He also ended the cooperation with Ågerup. The thought of buying yesterday’s technology from Ågerup while simultaneously financing the technology of tomorrow had no appeal. Ågerup was paid approximately 10 million French Francs for his work with Corneal including material, according to Gilles Bos. The formal recipient of the payment was a small company owned by Ågerup named Medinvent.

Gilles Bos absorbed everything worth knowing regarding producing hyaluronic acid from rooster combs during his sessions with Bengt Ågerup. He also absorbed everything Ågerup mentioned in passing regarding people and places that had influenced or been influenced by Ågerup’s knowledge. One such person was Mme Michèle Ranson, biologist and founder of the company Javenech SA, located outside Fougères in Bretagne. It eventually dawned upon Bos that it was Javenech SA that had supplied Ågerup with the necessary raw material in producing the non-animal, stabilized hyaluronic acid that had been placed on his desk. Gilles Bos reached out to Javenech, and Corneal began purchasing the same raw material.

Something Ågerup had never mentioned in his meetings with Bos was the intended purpose of the new type of hyaluronic acid. However, it was not long before Corneal understood that the new product was being marketed toward the cosmetics industry. When Q-Med released its revolutionary new product Restylane at the end of 1996, Corneal was in pursuit of the same market.

In 2000, just four years after Q-Med’s Restylane, Corneal was awarded CE certification for Juvéderm and Hydrafill®. Both products were based on hyaluronic acid produced by bacterial fermentation. Leading Corneal’s forward march were Gilles Bos and his team, which included Estelle Piron, among others, who was later to participate in the development of hyaluronic acid-based dermal fillers for other
companies on the cosmetics market. The technology behind the new production method was called Hylacross Technology. The successful introduction of Juvéderm onto the European market led the way for its introduction in the U.S. The U.S. market made very large gains almost immediately. It began, as previously mentioned, when Inamed acquired exclusive distribution rights for Juvéderm and non-exclusive rights for a few of the largest European markets. The breast implant producer Inamed was already in control distributing Hylaform and the collagen-based Zyderm and Zyplast.

The next step in Inamed’s development was its being purchased by Botox manufacturer Allergan at the end of 2005. Not content with merely owning Inamed, Allergan purchased Corneal in October 2006. At the time of the purchase, 75 % of Corneal was owned by its founder Waldemar Kita. Allergan paid 234 mUS$, of which Kita received approximately 175 mUS$. Yet another multimillionaire had been produced thanks to hyaluronic acid. Part of Kita’s earnings went to purchasing the French football club Nantes FC. After near immediate relegation to France’s Ligue 2, ”Les Canaries” are again playing in Ligue 1 as of the 2013 season. In an interestingly similar sequence of events, the Swedish football club from Uppsala, Sirius, has also been promoted ahead of the 2014 season under continued sponsorship from another hyaluronic acid multimillionaire, Bengt Ågerup.

With Allergan at the helm, Juvéderm sold for 388 mUS$ in 2012 and 478 mUS$ in 2013. In its annual report for 2011, it was proclaimed that Allergan possessed “the world’s No. 1 selling dermal filler brand”.

The bold claim made by Allergan is unverifiable, as Q-Med’s owner, Galderma, refrains from presenting sales for individual products in its annual reports. What is verifiable is that Galderma considers Restylane to be one of its eight strategic brands which sell for at least 100 million Euros each, according to their annual report from 2011. When Medicis’ sales of Restylane and Perlane on the American market are taken into account, the amount grows by 181,6 mUS$. Market researchers Evaluate Pharma estimate global sales of Restylane during 2011 to be 345 mUS$.

In the previously mentioned email correspondence with Bengt Ågerup in October 2014, his relationship with Corneal is described as follows: ”Corneal, who had been selling Microvisc in France, started to develop a product of their own and got into problems. Q-Med helped them in solving these problems. Through this Gilles Bos picked up a thing or two, which eventually led to Juvéderm for the aesthetics market. However, they didn’t manage to imitate Q-Med’s Restylane. Instead, they had to do with a method published by Laurent in 1963.”
Q-Med and Restylane – a side project that lead to riches

On October 18, 1999, Q-Med’s then CEO Per Olof Wallström released a statement to the press. He announced that Q-Med and other involved companies had reached a settlement in a lawsuit that had been initiated by Biomatrix, Inc. in a New Jersey federal court in May of the same year. The statement made clear that neither of the parties involved took any responsibility in terms of the conflict itself. However, as part of the settlement, Q-Med agreed to grant Biomatrix an exclusive license for certain technology. The license was to be global in nature, exclusive to Biomatrix and free from fees and royalties. In addition, Biomatrix was promised a sum of 100,000 US$ as well as royalties on the order of 6% pertaining to Q-Med sales in the U.S. on certain specified products, or a maximum of 5 mUS$. The statement ends: “The conflict is resolved and can only be brought back into question in the event that Q-Med significantly breaches the terms of the newly reached settlement.”

In a series of interviews about the conflict, Ågerup has said what he expressed in the periodical Veckans Affärer in the December 6, 1999 issue: ”It was almost like being sued by one’s own father.” In the previously mentioned interview in Kemisk Tidskrift (2001) he made the following comment about the conflict with Endre Balazs: “We have settled our dispute. There was no real good reason for him to sue me. But in the U.S. they sue anyone for anything.”33

The conflict delayed Q-Med’s introduction to the stock market by six months. In the previously quoted book Svenska Miljardärer (“Swedish Billionaires”) by Birgitta Forsberg from 2012, Ågerup gives insight into his thoughts and actions during the spring of 1999 as legal negotiations with Biomatrix were about to commence:

”The CEO for Biomatrix, Rory Riggs, is quite boisterous. If he is sitting in a restaurant for example, everyone hears exactly what he is saying. He had a summer house in upstate New York. Our attorney had a house there as well. He used to ride his bicycle and stop outside of Rory Riggs house. He would hang around for a while and listen to Riggs speaking on his mobile phone, getting updates on our counterpart’s next course of action. It could be called our intelligence operation. Our law firm thought we should offer Balazs what it would cost to bring about a settlement, 5 million dollars.”

Regarding the terms of the settlement involving Q-Med compensating Biomatrix with royalties for certain products on the U.S. market worth 5 mUS$, Ågerup makes the following comment: ”We earned that back in three months.”

33 In Swedish: ”Vi har förlikats. Han var helt enkelt ute i ogjort väder. Men i USA är ju kulturen sån att man stämmer varann i tid och otid.”
Although Bengt Ågerup likened the experience to being sued by one’s own father, it was hardly Balazs himself that led the charge against Ågerup and Q-Med. Rather, it was Balazs’ closest collaborators and the company’s board that demanded action. Biomatrix’ Board of Directors included Kurt Mark, the former chairman of Pharmacia’s Board of Directors, who, according to Ågerup, Balazs had invited to become a member of Biomatrix’ board on Ågerup’s recommendation. Ågerup had got to know Kurt Mark in Paris, and considered him to be a close friend. Ågerup was, in other words, sued by a person he looked up to, and the suing was insited upon by another person, who he regarded as a close friend.

Many executives at Biomatrix had reacted with extreme displeasure when they came to learn that a fellow colleague and the CEO of Biomatrix’ Swedish affiliate had secretly developed a rival product that had now received a patent and was introduced onto the market. Before the decision to bring forth litigation against Q-Med for patent infringement, there was extensive research into Ågerup’s activities parallel to his time as CEO for the Swedish affiliate. It had been revealed that Ågerup had simultaneously set up clinical trials for both Hylaform, on Biomatrix’ behalf, and for his own product, Restylane. Moreover, Ågerup had set up clinical trials for both products with the same German specialist. A more detailed presentation of the parallel projects run for Hylaform and Restylane in Germany in the early 1990s, and Bengt Ågerup’s dual roles, follows in the next section.

That Bengt Ågerup was also involved in the development of hyaluronic acid-based products for the eye surgery market, i.e. products competing with Healon, was something Endre Balazs and Biomatrix had become aware of through the “Canadian incident” in 1993 (see above). In 1995, Ågerup was questioned by colleagues at Biomatrix as to his possible involvement in Bohus BioTech AB in Strömstad. In a fax from March 28 of that year, there is a clip from a Swedish newspaper saying that the German company Merck has purchased 50% of Bohus BioTech AB’s total stock. The seller of the stock is the company Ågerup & Ågerup AB. On the fax is a hand scribbled note by Bengt Ågerup that reads: "Not my company! It is owned by Ingrid and Göran Ågerup." The fact that Bengt Ågerup had started the company, and owned 50% of it well into 1994, was something that remained unknown to Endre Balazs and others at Biomatrix.

Interviews with both Balazs and his closest co-workers at Biomatrix make clear that Endre Balazs was likely the least upset of the bunch. The seemingly indifferent, or lenient approach by Balazs in regards to Ågerup’s actions can be explained by two factors. First, Balazs was largely uninterested in the cosmetics market at the time, as well as other forms of hyaluronic acid, aside from those which were rooster comb-based. Rather, he was fully focused on Synvise. Strongly contributing to his disinterest
were the rising sales of Synvisc around 1996/97, thanks, in part, to the financial input by Up-Will Investor KB, a company initiated by Bengt Ågerup.

Secondly, he had a basically positive attitude toward Ågerup. He particularly appreciated Ågerup’s creativity. "I kind of liked him,” explained Balazs concisely while describing his feelings toward Ågerup during their years of collaboration, during a discussion I had with him in September 2013. As it seems, Ågerup’s paternal like feeling from Balazs was strikingly accurate.

Despite his mixed feelings as to what action should be taken against Ågerup, Balazs had no choice. Biomatrix had been listed on the New York Stock Exchange since July 1998. As CEO, his primary responsibility was to protect the interests of his shareholders. Patent infringement was a transgression that was impossible to ignore. Furthermore, not responding to such a violation would be a clear breach in Balazs’ duties as CEO, something punishable by law in the U.S.

The controversy with Biomatrix did not prove to be a major obstacle in the development of Q-Med and Restylane. The table below makes this fact visually apparent. It begins in 1996, the year Restylane was introduced on the market. The settlement with Biomatrix was reached in 1999. Q-Med made its debut on the stock market the same year. In 2005, a year had passed since Medicis had released Restylane in the U.S, and in 2011, Q-Med was acquired by Galderma.

As seen in the table, Q-Med grew at its fastest during the years 2000-2005, despite the fact that the U.S. debut was not until 2004. An important note in regard to the slowed growth during 2005-2010 is the increased competition in Europe and the U.S. brought about by the introduction of Juvéderm, a product which would have likely never seen the light of day without Bengt Ågerup’s tutoring sessions at Corneal in 1992-1994.

<table>
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*Q-Med’s development 1996/97-2010*

At the onset of 2011, Q-Med was purchased by the Swiss company Galderma, specialists in dermatology and owned by Nestlé and Oreal. The final price was 1.22
billion US$\textsuperscript{34}. Ågerup’s ownership share of Q-Med at the time of Galderma’s acquisition was 47.5 per cent. Had he not been a multi-millionaire before, he certainly was now.

\textsuperscript{34} Bloomberg News, Feb 10, 2011
CHAPTER 24: A pioneer in the early development of Hylaform and Restylane

As referred to earlier, during legal proceedings between Biomatrix and Q-Med/Bengt Ågerup in 1999, it became known that Ågerup had simultaneously been involved in projects regarding both Hylaform and Restylane in Germany. Specifically, he had recruited the same plastic surgeon for testing of Restylane who had previously been hired by Biomatrix to test Hylaform. The first person to realize what had happened was Johann Scheidt, Vice President of International Operations at Biomatrix. Scheidt had, among other things, been involved in the CE certification of Synvisc and Hylaform in Europe. During the 1999 legal proceedings, he suggested that Reinmüller be called upon as a witness. His suggestion was not accepted.

After having interviewed Johann Scheidt in August 2014, information was revealed that necessitated further investigation regarding Johannes Reinmüller and his role in the development of Hylaform and Restylane. Among other things, I found that Reinmüller was quite possibly the first person to describe the use of hyaluronic acid as a dermal filler. His account was delivered at the “5th annual meeting of the German association for aesthetic medicine” in Lindau, September 1992. The title of Reinmüller’s lecture was “Die Anwendung der Hyaluronsäure als Biomaterial in der plastischen und ästhetischen Chirurgie” ("The use of Hyaluronic Acid as Biomaterial in plastic and aesthetic surgery"). I also found a reference online regarding an article that was never published entitled: "Q-Plast, Studie bei Patienten mit Falten und Narben. Sponsor: Q-Med, Uppsala, Schweden" ("Q-Plast, a study of patients with wrinkles and scars. Sponsor: Q-Med, Uppsala, Sweden")35.

Once I had reached this point in my research of Johannes Reinmüller, I decided to contact him in hopes of a meeting. Reinmüller responded and we decided to meet the following Sunday in late September, 2014. We met at the airport in Frankfurt and began by having lunch at an Italian restaurant in Wiesbaden, where Reinmüller told me:

“This restaurant, and another in Wiesbaden, La Perla, were frequent meeting places for myself and Bengt Ågerup from 1990 until 1996. Sometimes it was just the two of us, other times we met together with my colleague Hans Schwall. We were also joined occasionally by Dr. Schneider from the company Kilfo. Kilfo was in charge of

35 http://www.fillerwelt.de/veroeffentlichungen/literatur.html
registration administration for Synvisc and Hylaform initially, and later even Restylane.”

After lunch, we decided to go to Reinmüller’s office, Klinik am Sonnenberg, where he continued his story.

Johannes Reinmüller came in contact with Biomatrix at the beginning of 1989, when introduced by Hans Schwall to the earlier mentioned Dr. Schneider. Schwall represented a company that sold silicone implants and surgical instruments, and Dr. Schneider was involved in work with Biomatrix at the time. Though Schwall was not involved with Biomatrix, he and Bengt Ågerup had known each other for some time. According to Reinmüller, Ågerup and Schwall had summer residences close to each other in the Grimaud area on the French Riviera.

At first, the conversation between Johannes Reinmüller and Dr. Schneider focused on possibly using Synvisc or hylan B in combination with reconstructive breast surgery. At some point, the conversation changed course at Reinmüller’s initiative, as he speculated on the opportunity to use Synvisc or hylan B instead of collagen for treating wrinkles. Reinmüller had tested the collagen-based product Zyderm II, but was dissuaded by the allergic reactions that had occurred.

Dr. Schneider would go on to apply for, and receive proper authorization to test hylan B in 1991, with Dr. Reinmüller as performing clinician, making him one of the very first to inject Hylaform (as the product came to be called) as a wrinkle reducer.

Biomatrix was first represented by a Swedish consultant, but after Johannes Reinmüller and Bengt Ågerup met in late 1990, Ågerup assumed responsibility for Biomatrix’ contact with Reinmüller.

It was Johannes Reinmüller’s collaboration with Biomatrix that lead to his participation in the previously mentioned congress in Lindau. Bengt Ågerup was present during Reinmüller’s lecture, which described experiences with Hylaform for his German colleagues within plastic surgery. Immediately after the congress, a letter of intent was signed by Bengt Ågerup, Johannes Reinmüller and Hans Schwall. It stated: “Biomatrix Sv. AB is negotiating in good faith and exclusively with Mr. Schwall and Dr. Reinmüller regarding the rights to distribute the product Hylaform in Germany.”

In anticipation of exclusive German sales rights for Hylaform, Reinmüller and Schwall started a company named Daedalus Gmbh.

In December 1992, Biomatrix and Johannes Reinmüller signed a confidentiality agreement concerning a possible clinical investigation, aimed at aiding the coming
process of Hylaform registration in Germany. In March 1993, a letter of intent was
signed by the three firms Daedalus Gmbh, Kilfo Gmbh and Biomatrix, Inc. regarding
future sales of Hylaform in Germany. Biomatrix was to act as producer, Kilfo as
importer, and Daedalus as distributor. The signer for Biomatrix, Inc. was Endre Balazs.

Kilfo Gmbh submitted an application for registration in 1993 to the regional German
authorities, but the application was not pursued any further, as the result of changing
EU legislation. Instead, it was decided that it would be more appropriate to apply for
CE certification, valid for all of Europe. However, this procedure would require
additional documentation.

During the autumn of 1993, negotiations were undertaken between Daedalus Gmbh
and Biomatrix, Inc. regarding distribution rights for Hylaform in Germany. Discussions were based on the letter of intent signed earlier the same year. During the
talks, Biomatrix, Inc. was represented by the manager for their European office, John
Feilders. Biomatrix presented a proposal that left Reinmüller and Schwall
unimpressed. It was described as: “Twentyfive paragraphs telling us what to do and
five paragraphs describing Biomatrix’ responsibilities.” Reinmüller and Schwall
contacted Bengt Ågerup in order to express their concerns with the offer from
Biomatrix. To their surprise, Ågerup advised them not to sign the agreement. Instead,
they should wait for an even better product that Ågerup was developing outside of
Biomatrix.

The alternative product offered by Ågerup

Upon continued discussions between the three, Reinmüller and Schwall learned that
the product Ågerup alluded to was Q-Plast. Q-Plast was based on hyaluronic acid
produced by bacterial fermentation which had been developed by Q-Med in Uppsala.
After having initially negotiated with Bengt Ågerup, CEO for Biomatrix Svenska AB,
Johannes Reinmüller, Hans Schwall and Dr. Schneider now found themselves in the
midst of a deal with Q-Med AB, also through discussions with Ågerup, who happened
to be owner and CEO of Q-Med.

On January 6, 1994, Klifo Gmbh submitted an application for authorization to perform
clinical trials of Q-Plast. In a letter from Klifo to ”Der Regierungspräsident” in
Darmstadt a few days later, it is clarified that the trials will be supervised by Dr.
Johannes Reinmüller in Wiesbaden. The application is successful, and clinical trials
on 111 patients are performed from July until November the same year.

Before trials began, Reinmüller and Ågerup discussed an appropriate brand name for
”Q-Plast”, which was considered internal jargon. According to Reinmüller, the name
"Restylan" or, as the product would later be spelled, "Restylane", was his idea. As proof he showed me a copy of a fax from Ågerup to Hans Schwall dated April 28, 1994 which read: "Talked to Johannes. The name is RESTYLAN™. We can add a prefix or other things to indicate a stronger action."

Though clinical trials were performed as scheduled, Reinmüller received a letter from Ågerup on December 8, 1994 that said: "The quick route (Darmstadt/Schneider) to approval has collapsed." Despite such negative news, the letter also contained a draft letter of intent between Q-Med and Daedalus Gmbh regarding distribution rights for Restylane in Germany, Austria and Switzerland. Interestingly, Ågerup goes on to express doubts about Daedalus Gmbh’s ability to successfully manage such a large undertaking. He therefore proposes that he and Reinmüller: "... form a good venture in exploiting a number of inventions both you and I have in plastic surgery."

Reinmüller declined Ågerup’s offer, based partially on reasons of loyalty. Despite Ågerup’s concerns, an agreement regarding German distribution rights for Restylane "and related tissue augmentation products" is signed a year later, in December 1995. Signers for Daedalus Gmbh are Johannes Reinmüller and Hans Schwall. Ågerup also signed the agreement, though not on behalf of Q-Med, but rather for Brixton Medical AB, another Ågerup-owned company. Worth noting, at the time of the agreement, Biomatrix, Inc. had just received CE approval for Hylaform.

In June of 1996, Biomatrix agreed to a deal allowing Collagen Inc. to assume European sales rights for Hylaform in exchange for 5 mUS$. Collagen Inc. went on to introduce Hylaform onto the European market in November 1996. Evidence of this can be found in a press release by Biomatrix dated November 11, 1996.

Collagen’s Hylaform introduction was preceded by a planning meeting in Paris in September 1996 between representatives for Collagen and Biomatrix. The meeting is mentioned in a letter from Bengt Ågerup to Johannes Reinmüller dated September 23, 1996 that contained the following:

"I need to know if you are coming to Paris this week-end. ... We have a domestic meeting (Nikko Hotel) where Hylaform (I think they will call it Hylan Gel) will be introduced. At that meeting we will quietly interact to pick up the position of Collagen and make new friends. ... Otherwise, the actual launch of Restylane will have to wait to a meeting where we can plan ahead. France is a bit special."

When Ågerup uses the pronoun "we", he is apparently referring alternately to Biomatrix, and Q-Med, as he was CEO for both companies while actively working to develop competing products. Biomatrix’ goal with the meeting in Paris was to transfer as much information and knowledge as possible to Collagen in order to ensure a successful introduction of Hylaform. According to Johan Scheidt, both Endre Balazs
and Janet Denlinger were present at the meeting, and very few people at Biomatrix knew of CEO Ågerup’s efforts to develop a competitor.

The following month, in October 1996, Q-Med was awarded CE certification for Restylane. On October 14, Hans Schwall was called to a meeting on October 18 in Paris. In his invitation, Ågerup explains that he is to travel to Uppsala the following week in order to explain “the German plan.” The meeting takes place with Johannes Reinmüller representing Daedalus Gmbh instead of Hans Schwall. During the course of the talks, Ågerup makes Reinmüller the same offer he had received in December 1994, namely the opportunity to work forward with Ågerup without involving Schwall. Reinmüller once again declined Ågerup’s offer, insisting that the contract between Daedalus and Brixton Medical be respected.

A few days later, a letter from Ågerup addressed to Hans Schwall/Daedalus is received written on Brixton Medical’s letterhead. It contained the following:

“… Q-Med is not prepared to take over the contract you and I wrote with Brixton Medical AB. Their attitude is that the contract is not valid and that they do not want to write a new one with you due to lack of performance in the cosmetic field. So as I told you, you should have worked with the market plan to be impressive to Q-Med!” The letter concludes: “… I hope that this will not disturb our other fields of co-operation! For your information I send this on B-M’s letterhead in case you want to move into a legal action against the company.”

The letter was of no surprise to Johannes Reinmüller. He had become suspicious of such an outcome during his meeting with Ågerup a week earlier. And it also became clear why Ågerup had signed the distribution agreement with Daedalus on behalf of Brixton Medical instead of Q-Med, as the company had no assets to speak of. Reinmüller acknowledged: “I knew this was the kick out of Daedalus and the end of a long lasting intrigue. I left Paris without any perspective.”

Johannes Reinmüller consulted his attorney in Wiesbaden about the possibility doing just that which Ågerup had proposed, namely, taking legal action. Such action was decided against, as Brixton Medical had no assets. As Reinmüller expressed the matter: “I preferred to go on with my plastic surgery and to be free for further developments in the field of hyaluronic acid.”

Reinmüller’s early experiences with Hylaform and Restylane had inspired him to continue working with hyaluronic acid, both at his clinic and as a consultant. He has been recruited by German pharmaceutical giant Merz in order to assist in the development of Belotero, among the strongest competitors to Restylane and Juvéderm on the American market today. He also holds a number of patents based on hyaluronic acid, one of which is for the treatment of skin or mucous membrane irritation.
The collaboration with Reinmüller and Schwall from Bengt Ågerup’s perspective

I have asked Bengt Ågerup to comment on his collaboration with Reinmüller and Schwall in the development of Hylaform and Restylane (in October 2014). He responded that they had collaborated on several projects, most of them linked to Biomatrix: implants and fillers. The results were poorly documented and not possible to use for registration purposes. According to Ågerup, Johannes Reinmüller was offered royalties for the German market for three years (for Restylane, as I understand it). Ågerup does not mention the reason behind this offer. In any case, the offer was turned down by Reinmüller, since he, according to Ågerup, wanted to develop a product of his own.
CHAPTER 25: Spin-offs generate yet more spin-offs

One of the most important considerations for a company utilizing unique knowledge in its products is insuring that such knowledge does not find its way into unauthorized confines. The disclosure of sensitive information within a company can occur by way of mere carelessness. One example would be an employee offering information that would make it possible for a competitor to simply copy a product or method of production. Disclosure can also be the result of spying and knowledge theft, performed by so-called “insiders.” The most common disclosure of sensitive information is supposedly caused by key players who either jump ship or are forced out of a certain company. Bohus BioTech could be described as having been a product of all of these factors. Of the company’s four original founders, two had chosen to leave Pharmacia (Daniel Ogbonnaya and Hans Åkerblom) and one had been forced from the company (Bengt Ågerup).

Pointedly, Bengt Ågerup was CEO for Biomatrix’ Swedish affiliate while he was simultaneously creating Bohus BioTech. As earlier noted, Ågerup’s activities surrounding Bohus BioTech were completely unbeknownst to Biomatrix. In precisely the same manner, Ågerup’s teaching sessions at Corneal were not known at Bohus BioTech. One is left to wonder what, if anything, a company can possibly do in order to prevent such spreading of sensitive knowledge.

Bohus BioTech, as well as Ågerup himself (and Q-Med) could be described as spin-offs from Pharmacia Ophthalmics and Biomatrix. What all of these companies have in common is Endre Balazs and his knowledge of producing hyaluronic acid. Juvéderm can certainly be described as a spin-off from Bengt Ågerup, which in turn paved the way for yet more products based on hyaluronic acid. Among those having seen their chance as a result of Juvéderm are Anteis, with products Esthéli and Belotero Balance; the company Teoxane, with its Teosyal; and even Pierre Fabre and Laboratoires Vivacy with Glytone fillers and Stylage.

Anteis

The company Anteis was formed 2003 in Geneva by Gilles Bos, Ågerup’s eager apprentice at Corneal, and Bos’ second wife Silvia Scherer, together with three former colleagues at Corneal. By 2002 Gilles Bos had, according to himself, grown weary of working with Waldemar Kita and took up a position as Vice President of the Allergan-owned Advanced Medical Optics (AMO) in Santa Ana, California. Allergan had sought to remove itself from the ophthalmology market, leaving AMO to its own
devices. One of the main tasks bestowed upon Bos was performing due diligence on Pfizer with regard to their ophthalmology endeavors. Of most notable interest was Pfizer’s product Healon, a product Bos recently had provided with further competitors on the market. Bos’ study resulted in AMO purchasing Healon and other related products from Pfizer. While Bos continued to labor at Allergan/AMO, commuting between Europe and California, his wife was fired from Corneal’s German affiliate by Waldemar Kita. This proved to be the catalyst for forming Anteis, an effort to utilize Silvia Scherer’s substantial experience with hyaluronic acid-based products. Bos then saw an opportunity to end his arduous commute and break from Allergan. He began to work as Anteis’ CEO after approximately a year. However, before his work at Allergan/AMO was finished, he completed a task he had been assigned in writing an analysis of the global cosmetics market. His final advice to Allergan, despite his no longer very warm feelings for Waldemar Kita, was: buy Corneal! This piece of advice was followed a few years later, and Allergan thus obtained Juvéderm, a product Gilles Bos had actively participated in the creation of, as a complement to Botox Cosmetic.

With the knowledge Gilles Bos, Silvia Scherer and their three co-founders had gained from Corneal, Anteis was able to develop its own, patented production method of biofermentation, named CPM (Cohesive Polydensified Matrix). During its ten-year existence, the company has grown to 150 employees and is active within all three main markets for hyaluronic acid: ophthalmology, orthopedics and cosmetics. Though most production is performed utilizing the CPA platform, Anteis even sells Ophteis®, a line of products produced from rooster comb- based hyaluronic acid supplied by Bohus BioTech.

Manufacturing and selling hyaluronic acid-based products in Europe today is hardly the privileged enterprise of the past. Up until the start of March 2012, there were no fewer than 110 dermal fillers on the French market with approval from Afssaps (l’Agence française sanitaire des produits de santé) according to French periodical Marianne.36 Receiving approval from the American FDA is a more strenuous affair. To the same point, no more than six dermal fillers had received FDA approval. Among the exclusive group is Belotero Balance, sold by Merz Pharma under license by Anteis; also known as Esthélis and Fortélis when sold by Anteis directly. When Belotero Balance received approval in November 2011, it became the fourth hyaluronic acid-based dermal filler of Healon ancestry to get FDA-approval. The three predecessors have been mentioned above: Hylaform, Restylane/Perlane, and Juvéderm.

In November 2013 was announced that Anteis had been acquired by its licensee on the U.S. market, Merz Pharma. The amount paid has not been revealed, but the Swiss

36 Marianne (Feb. 2012)
business magazine Bilan37 believed the price to be at least twice as high as Anteis’ total revenues in 2013, which were expected to exceed 50 mUS$. As owners of 37.5 percent of Anteis, also Gilles Bos and his wife Silvia Scherer thereby have qualified as members of the illustrious club of MTHA – Multimillionaires Thanks to Hyaluronic Acid.

Teosyal, Glytone and Stylage

Teosyal
Based in Geneva and started in 2003 by Valérie Taupin, Teoxane could be readily described as another spin-off of Corneal. Taupin was in the aftermath of an extremely uneasy time as CEO for Lea Derm. She had been appointed there as part of a joint venture with Corneal. The enterprise entailed close cooperation between the two companies, as Taupin owned 49 % of Lea Derm, and Corneal 51 %. The main purpose of Lea Derm was to market Corneal’s Juvéderm, which had received CE certification in year 2000, the same year Lea Derm was created.

The close working relationship with Corneal meant Taupin worked closely with Corneal’s owner, Waldemar Kita. The two did not collaborate well and Taupin was fired by Kita in 2003. She responded by suing Kita and was eventually awarded close to 3 million Euros in damages, according to Le Parisien38. Following the legal action against Kita, Taupin started Teoxane. Production began immediately on a variety of products. One product in particular has had significant success on the European market, dermal filler Teosyal. The product is reportedly manufactured using much the same method as that of Juvéderm.

In August 2013, Alphaeon Corporation revealed that they had: “… acquired an exclusive United States license for the full line of products from Geneva-based Teoxane Laboratories.” It was also announced that Teoxane’s founder and board president, Valérie Taupin would join the board of Alphaeon. An FDA approval application for Teosyal has now been submitted and awaits a decision.

37 Bilan (Dec. 2013) 13 December 2013: ”Le genevois Anteis rejoint le giron d’un groupe allemand”
38 Le Parisien (September 12, 2008)
Biochemist Estelle Piron had worked closely with Gilles Bos at Corneal and even with Valérie Taupin. She was largely involved in the developments surrounding Juvéderm. After leaving Corneal, she began work at Institute de Recherche Pierre Fabre (IRPF) where she developed the dermal filler that later was sold under the brand name Glytone. In May 2012 Pierre Fabre signed a partnership agreement with Merz Pharma through which Merz became owner of the global rights to Glytone’s injectable hyaluronic acid products and the non-US rights to other products of the brand.

In 2007 Estelle Piron started Laboratoires Vivacy together with two former colleagues at Corneal, Guy Vitally and Michel Cheron. The main product of Vivacy is the dermal filler Stylage, which has received rapid success on the European market. A fourth probable partner of Laboratoires Vivacy, judging from an article in the French web journal Entreprendre39, is Piron’s, Vitally’s and Cheron’s former boss at Corneal, Waldemar Kita.

CHAPTER 26: What became of Hylaform?

As described above, Biomatrix created the first hyaluronic acid-based dermal filler, Hylaform, which was launched on the European market in November 1996 by Collagen Inc. After this, a series of events took place, and a number of decisions were made that hampered the product’s advantage of being first to market. In December 1997, for reasons largely unknown, Biomatrix decided to withdraw its Pre-Market Approval application for Hylaform with FDA. This is briefly mentioned in Biomatrix’ 1999 Annual Report: “The Company is in discussion with FDA to start a new trial in the United States in order to obtain U.S. approval for Hylaform.” As a result of this, FDA approval was not obtained until April 2004, four months later than Restylane.

It can be reasonably assumed that the decision to award licensing rights to Collagen Inc. had negative implications for Hylaform, as it became part of a product family which already had two similar “children”, namely the collagen-based fillers Zyderm and Zyplast. Judging from Hylaform’s limited market success during the years following Collagen’s acquisition of the distribution rights, one may suspect that Hylaform was treated as a “stepchild” in its new environment.

Two events that further complicated matters for Hylaform were Inamed’s acquisition of Collagen Inc. in 1999, and Genzyme’s acquisition of Biomatrix the following year. A light in the dark for Hylaform, though, is a press release from October 16, 2002, where Inamed and Genzyme Biosurgery announce that an agreement for Hylaform on the U.S. Market has been reached. The agreement, which includes Hylaform, Hylaform Plus and Hylaform Fine Line, is presented by Inamed as follows: “This agreement gives us the opportunity to expand our leadership position in the facial rejuvenation market in the United States beyond Zyderm and Zyplast, the current gold standard for dermal fillers.” The fact that Inamed and Genzyme Biosurgery as late as October 2002 refer to collagen-based products as “the current gold standard for dermal fillers” is surprising, to say the least.

The press release also mentions that Hylaform is undergoing clinical trials that are aimed at obtaining FDA approval. The approval is, as previously mentioned, obtained in April, 2004, four months later than Restylane.

Genzyme Biosurgery’s interest in hyaluronic acid was shown to go above and beyond avian-based Hylaform and Synvisc. Largely because of the positive reception of Restylane and Juvéderm on the European market, the company had started to develop a non-animal-based hyaluronic acid filler of its own. The company’s efforts were crowned with success, and on December 2, 2004, Inamed Corporation and Genzyme
Corporation\textsuperscript{40} could announce that “… the U.S. Food and Drug Administration (FDA) has granted market approval for Captique injectable gel – a new dermal filler product based on Genzyme’s non-animal stabilized hyaluronic acid (HA) technology.” The two companies also announced that: “Captique joins Inamed’s well-established U.S. dermal filler product franchise, comprised of Zyderm, Zyplast, CosmoDerm and CosmoPlast collagen\textsuperscript{41} and Hylaform and Hylaform Plus HA dermal fillers.”

As previously mentioned, Inamed had, as of January 2004, acquired exclusive distribution rights for Juvéderm in North America and Australia as well as non-exclusive rights for some of Europe’s largest markets. After Allergan’s acquisition of Inamed in 2005 and Corneal in 2006, and after Juvéderm had been approved by FDA in June 2006, Hylaform can be described as an insignificant member of an overpopulated family. During the period 2007-2009 a shakeup took place, resulting in Captique, Hylaform and all collagen-based products disappearing from Allergan’s product portfolio of dermal fillers. The only survivors were various products belonging to the Juvéderm dermal filler family.

The last time Hylaform is mentioned by Genzyme is in the annual report of 2009, in which the product is reported to have increased its gross product profit for 2008, as compared to 2007 due to: “… milestone payments received in 2008 for which there was no comparable amounts in 2007.” The payment is likely to have been made by Allergan as compensation for Hylaform’s withdrawal from the market.

\textsuperscript{40} Genzyme Biosurgery is since May 2003 reintegrated with the parent company Genzyme Corporation.

\textsuperscript{41} CosmoDerm and CosmoPlast were two collagen-based products licensed to Inamed by Smith & Nephew, Inc.
Part VI: Some final thoughts

My reason for writing this book is twofold. First, there is a story, or rather, a series of stories, linked to a magic molecule, that deserve to be documented for posterity. Secondly, I want to contribute to an increased understanding about important aspects of business life and innovation processes. “The Magic Molecule” itself might seem insignificant; “one swallow doesn’t make a summer”, as the saying goes, but it could be used to identify certain indications on a larger perspective. Often one swallow is followed by another.

In that sense there are great similarities between business literature and fiction; if book is added to book, example added to example, an increased knowledge will eventually develop that will help the reader better navigate in broad terms. The Magic Molecule can therefore be seen as part of a bigger picture. A story to be added to other stories about how research results can be transformed into usable products, about the way researchers manage their relations with licensees, about development processes which sometimes take different directions than planned, about employees who start competing businesses, and about companionship, loyalty, and deceitful behavior.

Two important aspects of business life and innovation processes that I want to discuss in light of the different experiences described in this book are Management of conflict and Factors for success.
CHAPTER 27: Management of conflict

Researchers trying to commercialize their research results by starting a company, or selling knowledge to an existing company should, according to The Magic Molecule, expect to face conflicts of different types. The same goes for companies attempting to extend their product portfolio by acquiring entire companies, or specific patent rights.

Particularly, larger companies should also prepare for conflicts with disloyal employees who start competing companies of their own, or are tempted to join competitors. Companies and individuals supporting innovation projects as risk capitalists or business angels should count on and prepare for different types of conflicts at different stages of the development process.

There are many examples of conflicts in The Magic Molecule. These conflicts have been managed in different ways and with different results depending on, among other things, the intentions, expectations and attitudes of the parties involved, the relative importance of the conflict, and the negotiation skills of the parties involved.

I have selected 16 conflicts for closer analysis. Aiding me in this, I have chosen a frequently used model in connection with conflict management; the TKI Model (the Thomas-Kilman Conflict Model).

The TKI Model was developed by Kenneth W. Thomas and Ralph H. Kilmann in the early 1970’s in connection with a doctoral program at the University of California’s Graduate School of Business. The model identifies five conflict-handling modes in relation to two underlying dimensions: assertiveness and cooperativeness.

The five conflict-handling modes are:

- **Avoidance** – which means that a conflict is ignored. A possible reason could be lack of time. There are simply more important things to focus on.
- **Accommodation** – avoid confrontation and let the opponent have his or her way, because of fear, or because you consider your sacrifices as limited.
- **Competition** – the aim is to win at any price, without considering the consequences for your opponent.
- **Collaboration** – the typical “win-win”-situation, where you struggle to find the best possible solution for all parties involved.
- **Compromise** – the middle-of-the-road solution which is not optimal for any of the parties, but good enough, at least in a shorter perspective, while waiting for something better to turn up.
Concerning the two underlying dimensions; **Assertiveness** indicates to what degree one tries to satisfy one’s own concerns. **Cooperativeness** is the degree to which one satisfies the other person’s concerns.

![Diagram of the Thomas-Kilman Conflict Mode Instrument]

**The Thomas-Kilman Conflict Mode Instrument**

Some of the 16 selected conflicts are between individuals, others between companies, and yet others between an individual or a group of individuals on the one side and a company on the other. Below is a brief presentation of the different conflicts and their respective classifications according to the TKI-model.

Conflicts related to Healon (Part I, II and III):

1. **Endre Balazs (Biotrics) – Kabi Pharmacia AB (1992):** Conflict due to Pharmacia’s alleged unwillingness to develop Healon for the human osteoarthritis market, resulting in the re-negotiation of the 1976 license agreement. Conflict handling modes: Competing (Balazs, 1a), accommodating (Kabi Pharmacia, 1b)

2. **Endre Balazs (Biotrics) – Pharmacia & Upjohn (1995-96):** Conflict concerning Pharmacia’s royalty payments due to disagreement concerning “FCS” (first commercial sale) and whether royalties should be calculated for partial markets or not. Conflict handling mode: Compromising

3. **Pharmacia’s and Balazs’ lawsuit against Med-Chem, 1989-91, for infringement of the Healon patent.** Conflict handling modes: Competing (3a) followed by compromising (3b).

4. **The personal conflict between the new CEO (J-E Engkvist) and the CSO (Bengt Ågerup) of Pharmacia Ophthalmics, 1983-84, which resulted in the CSO’s exit from the company.** Conflict handling mode: Competing.
Conflicts related to Biomatrix Inc. (Part III):

5. Biomatrix’ litigation in 1999 against Bengt Ågerup, Q-Med and “other involved companies” for patent infringement. Conflict handling mode: Compromising.
7. The Class Action Lawsuit filed in 2003 between shareholders of Genzyme Biosurgery, a majority of which were previous shareholders of Biomatrix, Inc., and Genzyme Corp., the company which acquired Biomatrix. Conflict handling mode: Compromising.
8. The defamation case between Balazs-Denlinger and three individuals, two of which were former employees. Conflict handling mode: Competing.

Conflicts related to Xalatan (Part IV):

9-10. Two conflicts (Stern and Camras) concerning claims of co-inventorship: Conflict handling modes: Competing (Stern, 9), avoiding (Camras, 10)
11-12. Legal disputes between Pfizer on the one hand and Alcon and Allergan on the other concerning the latanoprost patent. Conflict handling mode (both cases): Collaborating.

Conflict related to Bohus BioTech AB (Part V):

13. Conflict between the four founders of Bohus BioTech due to unforeseen side effects, financial problems and alleged disloyal behavior of one of the founders. Conflict handling modes: Compromising (three of the founders, 13a), avoiding (one of the founders, 13b).
14. Conflict between Pharmacia Ophthalmics and a former employee, concerning the right to start a competing business. Conflict handling mode: Accommodating.

Conflicts related to the facial aesthetics market (Part V):

15. Bengt Ågerup’s, through Brixton Medical AB, cancellation of Daedalus Gmbh’s distribution agreement for Restylane in Germany. Conflict handling modes: Competing (Ågerup, 15a), avoiding (Daedalus, 15b).
16. Legal dispute between Waldemar Kita, majority owner of Corneal and Lea Derm and Valérie Taupin, CEO and minority owner of Lea Derm, leading to the creation of Teoxane. Conflict handling mode: Competing.
Classification of the 16 cases based on conflict-handling mode

**Cases in the “competing box”**

Competing has been the dominating conflict handling-mode in 7 of the 16 cases. During case 1, which involved renegotiating the original license agreement of 1976, Endre Balazs chose a competing approach, while Pharmacia behaved in a more accommodating way. Balazs’ dissatisfaction was, as explained in chapter 3, based on Pharmacia’s lack of interest in the human osteoarthritis market. He had repeatedly demanded economic compensation and insisted on renegotiation of the license agreement. Balazs’ attitude was perceived by the new management of Pharmacia Ophthalmics as very threatening – he was said to “hold a sword over our heads” – and decided therefore to sit down at the negotiating table to “clear the air”.

One might think that Endre Balazs came out of negotiations on top thanks to his assertive and uncooperative attitude. Kabi Pharmacia, on the other hand, can be perceived as a bit too accommodating by making financial concessions in the order of approx. 6 mUS$. However, these concessions should be judged in the light of Kabi Pharmacia’s annual sales of Healon at the beginning of the 1990’s, which amounted to approx. 200 mUS$, with profits well above 25 percent. In order to protect a business of that size and profitability, maybe 6 mUS$ is not too much of a sacrifice.

In case 3, the conflict between Pharmacia and Endre Balazs on the one side and MedChem on the other, we see an example where the attacking side went from being uncooperative (3a) to becoming cooperative (3b). MedChem, a company started by a former co-worker of Endre Balazs at Retina Foundation, was initially convicted of patent infringement and prohibited to sell its hyaluronic acid-based product Amvisc on the U.S. ophthalmic market. After two years of further negotiations, a settlement was reached through which MedChem regained part of their sales rights on the U.S. market.
This was achieved by paying a lump sum of 12.2 mUS$ and a royalty on future sales. In his autobiography, Endre Balazs comments on the conflict with MedChem: “… we both made a mistake. We should have come to some agreement to avoid the cost in time and money of the long court procedure.”

Case 15a illustrates a conflict where one of the parties (Bengt Ågerup/Brixton Medical) behaves in a way which the counterpart (Daedalus Gmbh) perceives not only as uncooperative and assertive, but also as dishonest.

In the remaining cases that illustrate a competing behavior (cases 4, 8, 9 and 16), the attacking side has not been prepared to compromise. This goes for the CEO of Pharmacia Ophthalmics, Jan-Erik Engkvist in his conflict with Bengt Ågerup; Endre Balazs and Janet Denlinger in their conflict with the two former employees plus a third person slandering them; László Bitó in the conflict with the doctoral student Stern, who claimed co-inventorship; and Valérie Taupin in the conflict with her partner Waldemar Kita. Winning the dispute is important in relation not only to the counterpart, but also the surrounding world. The implicit message is: This is how we will strike back in all similar cases.

**Cases in the “collaborating box”**

Of the cases in this “box”, one has already been discussed; case 3b between Pharmacia/Balazs and MedChem. The other two cases of this box, cases 11 and 12, concern patent infringement, and in both cases the latanoprost patent (Xalatan) is involved. In case 11 it is the owner of the patent, Pfizer, who is on the attacking side, as they sue Alcon for patent infringement on their product Travatan. In case 12, Pfizer defends itself against Allergan, who tries to invalidate the latanoprost patent. Both cases are settled, and Alcon and Allergan are allowed to continue to sell their products in return for paying a sales-based royalty to Pfizer. In the case of Allergan, a considerable lump sum is also paid.

**Cases in the “avoiding box”**

Of the three cases placed in the avoiding box, one concerns Carl Camras’ very late request for co-inventorship of patent ‘353, the origin of the “blockbuster” Xalatan. László Bitó’s only countermeasure was to turn his request down and, at the same time, inform him about his right to bring the case to court. Camras made no further requests.

Case 13b refers to the behavior of one of the four founders of Bohus BioTech. When problems started to mount up in 1993 in the form of unforeseen side effects, financial
problems and conflicting views among the founders, he returned his shares, which represented a 25 percent ownership in the company, to one of the other partners and left the scene.

Case 15b characterizes the avoiding behavior of the partners of Daedalus Gmbh in response to Bengt Ågerup’s decision to deny them distribution rights for Restylane in Germany.

Cases in the “accommodating box”

In two of the 16 cases it seems relevant to describe an accommodating conflict handling-mode. One such has already been dealt with above; Kabi Pharmacia’s response to Endre Balazs request for economic compensation and renegotiation of the 1976 license agreement (1b).

The other case, No. 14, has to do with the position taken by the management of Pharmacia Ophthalmics when they realized that a former employee, Daniel Ogbonnaya, had participated in the start-up of a competing business. Part of the planning of the new business had most probably taken place while he was still employed. A factor contributing to Pharmacia Ophthalmics’s accommodating attitude is said to have been the fact that they needed Ogbonnaya’s signature for an important patent application.

Cases in the “compromising box”

The compromise in case 2, one of five cases placed within the “compromising box”, can be seen as the result of a sophisticated battle between lawyers. The underlying cause of the conflict is diverging opinions between Endre Balazs and Pharmacia & Upjohn concerning the royalties paid for Healon over the years. The conflict takes place as a long-lasting business relationship is about to end. Most of the people originally involved in starting and developing the business relationship have left the scene, and there is no real emotional investment left, neither positive nor negative. Aided by his lawyers, Balazs wants to get as much as possible of the little that remains of a 25-year-long cooperation with Pharmacia. The new managers at Kabi Pharmacia want to end the relationship as cheaply as possible. They have already demonstrated their point of view by prematurely terminating the research agreement with Biomatrix within ophthalmology. Endre Balazs and Kabi Pharmacia eventually leave it to their lawyers to handle the conflict. The matter is settled out of court. The final compromise is arrived at in a very rational and calculated way; the parties meet each other halfway.
Given the strenuous nature of conflicts 1 and 3 (the re-negotiation of the 1976 agreement and the Med-Chem conflict), it becomes apparent why Balazs chose to solve the conflict above, as well as later incidents (conflicts 5, 6 and 7) by way of compromise.

The conflict between Biomatrix on the one side, and Bengt Ågerup, Q-Med “and other involved companies” on the other (case 5), was primarily driven by Endre Balazs’ co-workers at Biomatrix. Endre Balazs had, in his role as CEO of a company listed on the New York Stock Exchange, no other choice than to take action against an alleged patent infringement, despite his friendship with Ågerup. Bengt Ågerup has, as seen above, claimed that it was almost as if he was sued by his own father. Solving the conflict by compromising can therefore be seen as a logical solution at the time.

Cases 6 and 7 are both so-called Class Action Lawsuits, where small shareholders try to assert their rights against big companies. Both cases end, as these cases often do, by settlement. Despite this, shareholders saw but a tiny share of what they originally demanded.
As shown in previous chapters, the Magic Molecule, i.e. hyaluronic acid, has given rise to a large number of successful products within different areas of application. A prerequisite for a successful product launch is the skillful management and integration of a multitude of factors. My aim here is to try to create a better understanding of the mainly successful development of nine products that have appeared in previous chapters. I do this by using an analytical model based on seven factors, which all start with the letter “P”. Eight of the products are directly linked to hyaluronic acid, and the ninth, Xalatan, is looked upon as a spin-off from Healon and hyaluronic acid.

The analytical tool I have chosen is an extended version of a frequently used models within market analysis, namely the 4 P’s-model, or, as it is often referred to, the marketing mix-model. The marketing-mix model was originally developed by Jerome E. McCarthy\textsuperscript{42}, and made world-famous by the best-selling textbook Marketing Management\textsuperscript{43} by Philip Kotler. The 4 P’s of the marketing-mix model stand for Product, Price, Place and Promotion.

In my analysis of the nine products I have added three P’s to the original four, namely People, Permission and Possession. By People I refer to individuals, or groups of individuals who have had a significant impact on the development of a particular product. Permission is used to analyze the importance of different types of governmental or institutional approvals for the successful launch and marketing of a product. By Possession, I refer to the importance of ownership, including changes of ownership, for a product’s success on the market. The type of owner I mainly refer to is the product owner, but in some cases it is also relevant to discuss ownership with respect to the one who holds the license for a product on a specific market.

Below I will briefly discuss the seven factors, one by one, with respect to their influence on the development of the nine different products presented in the table below.

### Product

Under this heading different products are examined with respect to how unique they are from an innovation perspective. Three types of ”uniqueness” are identified; radical

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\textsuperscript{42} McCarthy, Jerome E. (1960)
\textsuperscript{43} Kotler, Philip (1967)
<table>
<thead>
<tr>
<th>Product</th>
<th>Price</th>
<th>Place</th>
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<td>Q-Med Galderma (Medicis)</td>
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Description of eight HA-based products and Xalatan based on seven “P’s”
innovation, incremental innovation, and imitation. A radical innovation is a product that offers a new solution to an existing need, or a previously unrealized need.

By incremental innovation I refer to a product which represents a slightly revised or improved version of an originally radical innovation. This may improve its competitiveness on existing markets, but may also enable its introduction on a new market. Imitation is the mere copying of an existing product.

As shown in the table, three of the nine products are classified as radical innovations (Healon, Restylane and Xalatan), four as incremental innovations (Synvisc, Hylaform, Juvéderm, and Esthélis/Belotero) and two as imitations (Microvisc and Viscorneal). Few would question my classification of Healon and Xalatan as radical innovations. I have also classified Restylane as a radical innovation based on it being the first bacterially fermented hyaluronic acid to be used as a dermal filler. Synvisc and Hylaform resulted from the further development of Healon, carried out by Endre Balazs and Janet Denlinger together with colleagues at Biomatrix. Their research efforts generated hylan G-F 20 and the hylan B gel, used in the production of Synvisc and Hylaform, respectively.

Juvéderm can be seen as a further development of Viscorneal, a product the French producer of intraocular lenses, Corneal, learned to produce with the help of Bengt Ågerup. While Viscorneal was more or less a copy of Healon, Juvéderm was developed by the research director at Corneal, Gilles Bos, and his team. This was accomplished with no other assistance from Bengt Ågerup than a bottle filled with bacterially fermented hyaluronic acid, which served as a source of inspiration for Bos and his team. Their efforts were crowned with the Hylacross Technology, based on which Corneal could develop Juvéderm and start competing with Restylane on the global facial aesthetics market.

Esthélis/Belotero (basically the same product, but sold under different names in Europe and the U.S.), produced by the Swiss company Anteis, can be seen as a representative of a number of dermal fillers produced by companies that have spun-off from Corneal, for example Teosyal (by Teoxane) and Stylage (Laboratoires Vivacy). Anteis was started by Gilles Bos together with his wife and three former colleagues who had left or been let go from Corneal. The fact that Esthélis/Belotero is based on a technology called CPM (Cohesive Polydensified Matrix), which can be seen as a further development of the Hylacross Technology of Corneal, motivates the classification of Esthélis/Belotero as an incremental innovation instead of imitation.

Both Viscorneal, which has been touched upon above, and Microvisc, are imitations of Healon. In both cases, the “mastermind” behind the transfer of technology and
know-how making it possible for Corneal and Bohus BioTech to start producing competitors to Healon primarily on the cataract surgery market was Bengt Ågerup.

Price

The classification of the nine products with respect to their price strategies is based on Michael Porter’s Generic Strategies Model\(^\text{44}\). According to this model, a company has three options in gaining a competitive advantage; either by offering products similar to those of their competitors, but at a lower price, or offering products for which customers are prepared to pay a higher price. Profitability by offering a lower price can only be obtained by keeping costs lower than competitors. This strategic option is called “cost leadership”. The strategy making it possible to stay competitive despite a higher price is called “differentiation”. The third strategic alternative according to Porter is “focus”, and has to do with the scope of the business activity itself. Focus can be either as broad as an entire industry: cost focus, or as narrow as a specific segment: differentiation focus (see diagram below).

Since all the nine selected products are focusing on specific segments (i.e. narrow scope), there are only two strategies relevant to discuss with respect to their pricing, namely “differentiation focus” and “cost focus”.

<table>
<thead>
<tr>
<th>Strategic advantage</th>
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<tr>
<td>Product uniqueness</td>
<td>Low cost</td>
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<td>Broad</td>
<td>Differentiation</td>
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<td>Narrow</td>
<td>Differentiation focus</td>
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*Generic strategies according to Michael Porter*

For all the products based on radical innovation, i.e. Healon, Xalatan and Restylane, setting the right price has been an important issue, particularly during an initial stage when competition has been non-existent or very limited. The fact that the U.S. market has been of high importance for all these products, and that the very-difficult-to-

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\(^\text{44}\) Porter, Michael E. (1980)
achieve FDA-approval has been a prerequisite for entering the market, have made it possible to maintain a differentiation focus for these products for a relatively long time.

FDA’s quite restrictive approach when it comes to approving dermal fillers has made it possible to charge a high price not only for Restylane, the first hyaluronic acid-based dermal filler to be launched on the U.S. market in 2003, but also for the first challenger, Juvéderm, launched in 2006. The fact that Belotero Balance, the fifth or sixth hyaluronic acid filler to receive FDA approval in 2011, is sold at a price only slightly lower than that of Restylane and Juvéderm indicates that the price sensitivity of the facial injectables market is very low.

Setting the right price has been emphasized as an important factor of success by decision makers involved in the launching of Healon and Xalatan, as well as Restylane. Erik Danielsson mentions the doubling of the initial price, shortly after Healon’s introduction on the U.S. market in 1980, as a key factor when explaining the product’s tremendous success and profitability. In spite of the price increase, which was implemented against the will of the marketing department at the U.S. subsidiary, there was a steadily increasing demand for Healon.

A similar experience is told about Xalatan, for which product the launch price was increased from the originally intended 5 US$ to 30 US$ per bottle. The price increase was motivated by the fact that since Xalatan was approved as a second-line treatment, it would mainly be used in difficult cases, when no other medicines seemed to be effective. This assumption turned out to be correct, and this had a very strong, positive effect on Xalatan’s profitability.

“With a good product, you can charge a high price.” This is a lesson Bengt Ågerup learned while working with Healon at Pharmacia, and which he later applied in the pricing of Restylane at Q-Med. In the previously mentioned book “Swedish Billionaires” (2012) Ågerup claims that the price Pharmacia was charging for a syringe of Healon was forty to fifty times above the production cost. This was possible since the product was used in connection with a very expensive operation.

During his years with Q-Med Ågerup never accepted any price cuts. “On the contrary”, he says according to Svenska Miljardärer: “I have taken people by surprise by increasing the price. Good products can stand more than people in the organization believe. You must always be on your toes.”
Place

For all the products, except for the two imitated products, Viscomenal and Microvisc, the USA has sooner or later become the biggest and most important market. In the case of Healon and Xalatan, USA was the market where the products were first launched, which more or less coincided with FDA’s approval. Synvisc, Biomatrix’ principal product, could, for special reasons, be launched on the Canadian market in 1992, three years before the CE-mark for the European market was obtained, and five years before the product was approved by FDA and could be launched on the U.S. market.

FDA approval is in itself no guarantee for success on the U.S. market. Healon’s successful introduction on the U.S. market can at least partly be ascribed to the fact that Pharmacia had a well-established subsidiary in the U.S., located in Piscataway, New Jersey. In a similar way, the well-functioning collaboration between Pharmacia’s marketing offices in Uppsala and Piscataway, and Upjohn’s marketing office in Kalamazoo, Michigan, have been mentioned important factors behind Xalatan’s success on the U.S. market.

When Restylane received its FDA approval in 2003, Bengt Ågerup decided to entrust the U.S. market to a company already operating in the market instead of creating a sales organization of his own. The company he finally picked was Medicis Aesthetics Inc., founded in 1998 by Jonah Shacknai, that specialized in the production and marketing of dermatological products. Medicis acquired the distribution rights for Restylane and Perlane for the U.S. and Canadian markets by buying the company HA North American Sales AB from a subsidiary of Q-Med for 160 million US$. This amount included 29.1 mUS$ upon FDA’s approval of Perlane, which occurred in May 2007.

Acquiring the distribution rights for Restylane and Perlane seems to have had a very favorable effect on Medicis’ development. In 2003, the year of acquisition, Medicis had 311 employees and total revenues amounting to 247 mUS$. This can be compared with 2011, when Medicis had 646 employees, 97 of which working in the facial aesthetics sales force, and total revenues amounting to 721 mUS$. Total sales of “non-acne dermatological products”, to which category Restylane and Perlane belong, and where Restylane can be assumed to account for at least 60 per cent of total sales, amounted to approx. 230 mUS$\(^{45}\).

The successful development of Restylane, and also Perlane, on the U.S. market was most probably an important reason why the Canadian pharmaceutical company

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\(^{45}\) The quantitative information presented in this section is collected from Medicis Pharmaceutical Corporation’s Annual Reports (Form 10-K) of 2003 and 2011.
Valeant in 2012 decided to acquire Medicis for 2.6 billion US$. This was 2.5 times the price Galderma paid for Q-Med in 2010. The value of Restylane and Perlane on the North American market was further accentuated when in May 2014 it was announced that Nestlé S.A., the owner of Galderma, re-acquired all the rights for Restylane and Perlane, and also the rights for Emervel®, Sculptra and Dysport for the U.S. and Canadian markets, for 1.4 billion US$ in cash.

Promotion

Tools frequently used in the promotion of a product are advertising, sales promotion, publicity, direct marketing, and personal selling. Two factors that seem to have strongly influenced the design of the promotional strategies for the nine products analyzed in this section are their uniqueness, i.e. if they are pioneers on the market they are introduced to, or if they are challenging previously introduced products of a similar type, and the size of company introducing the product. Of the nine products, four: Healon, Hylaform, Restylane, and Xalatan can be classified as pioneers, and the remaining five: Synvisc, Microvisc, Viscorneal, Juvéderm, and Esthelis/Belotero as followers.

A common denominator for the promotional strategies of Healon and Xalatan is the strong focus on personal selling through opinion leaders in the initial stage. In the case of Healon this was achieved through the IOM (Intraocular Microsurgery) seminars, several hundred of which were arranged both in the U.S. and Europe early in the 1980’s. In the case of Xalatan, the leading glaucoma treatment specialists in the world were continuously informed about the development and availability of the product through László Bito’s, Johans Stjernschantz’ and Carl Camras’ regular participation in the annual conferences of ARVO (Association for Research in Vision and Ophthalmology) and ISER (International Society for Eye Research). Of key importance for the promotion of Xalatan was also the Strategic Product Plan, mentioned in chapter 4, which ensured a uniform promotion and marketing of the product on a global basis, which was instrumental for the upgrading of Xalatan from secondary to first treatment option.

Target-group oriented promotion and personal selling were important tools also in the launch of Restylane. In the previously mentioned interview with Bengt Ågerup in the Swedish magazine Filter (January 2011), the following description is given on how Restylane was launched on the French aesthetics market:

“Bengt and his wife soon realized that they had to be present at the capital of the beauty clinics: Paris. To avoid the temptation of returning home they sold the house in Uppsala and settled down in the French capital. The core of the little family firm consisted of
Bengt, Helen, a daughter, the nanny and the piano teacher. Helen and the piano teacher established the new business, the daughter stamped promotion material, and the piano teacher called the beauty clinics to get to know the market. The beauty clinics received the hyaluronic acid with open arms. It didn’t cause any allergic reactions or other complications, it wasn’t of animal origin, and – contrary to collagen – it remained under the skin.”

Hylaform differs from the other pioneering products by the absence of a well thought-out promotion strategy. This can be explained by the low priority the product had in its original (Biomatrix) as well as in its new environment (Collagen Inc.). The fact that Hylaform represented a revolutionary technology for eliminating wrinkles was not recognized by Collagen Inc., who continued to refer to its obsolete technology (i.e. collagen) as “the gold standard for dermal fillers”.

Another thing to Hylaform’s disadvantage was the fact that Bengt Ågerup, in his role as CEO of Biomatrix Svenska AB, was fully informed about Collagen’s marketing plans for Hylaform on the French and European markets. He participated in, among other things, the meeting between Collagen Inc. and Biomatrix in Paris in September 23, 1996, at which the launch strategy for Hylaform in Europe was discussed.

Launching a follower on the market, i.e. a product that is challenging the market position of previously launched products, can be said to be easier than launching a pioneering product. While the company launching a pioneering product has to inform and convince the market about the new idea or the new technology on which the product is based, the follower can simply be promoted as either cheaper or better than the pioneer. The promotion strategy of a follower will most likely be strongly influenced by which pricing strategy that has been chosen and what market segments that are being addressed. If a company approaches the same market segments as the pioneer, it has either to claim that it is offering the same quality at a lower price, or a better product at the same or higher price. If new market segments are addressed, for example, offering dermal fillers not only to the most exclusive beauty salons in the bigger cities, but also to ordinary beauty salons in smaller towns, a lower price can be assumed to be of importance.

When Synvisc was launched on the osteoarthritis market, Japanese Seikagaku and Italian Fidia were already there with Supartz and Hyalgan. Synvisc was not offered at a lower price than its competitors. Instead the product was promoted as a better alternative from a qualitative perspective. Similar promotion strategies seem to have been used for Juvéderm and Esthéliis/Belotero, both products followers to Restylane on the dermal filler market. Both products have been offered to more or less exactly the same market segments as Restylane, at a similar price, but claiming superior qualities.
Viscorneal and Microvisc, both copies of Healon and primarily intended for the ophthalmics market, have somewhat different origins. Viscorneal was developed by Corneal to serve as a complementary product in the marketing and selling of the company’s intraocular lenses. Microvisc, on the other hand, was, and still is, offered as a viscoelastic device to be used by ophthalmic surgeons in connection with implantation of intraocular lenses, independent of what types or brands of IOL’s are used by the surgeon. Even if quality aspects are mentioned in the promotion of these two products, their implied competitive advantages are cost- and price-related.

**People**

In Chapter 11 I touched upon the role of individuals and groups of individuals regarding the outcome of innovation processes. People contribute in different ways and during different stages in a product’s development, spanning from initial idea to established product. Some people contribute continuously to a product’s development. This is frequently the role of the entrepreneur. Others make temporary interjections, which sometimes prove crucial for the final result.

To make a reasonably systematic analysis of different key persons’ contributions to the development of the nine selected products, I have identified 10 different roles that can be present during the development process, either entirely or periodically. The ten roles are:

*Inventor, Innovator, Entrepreneur, Imitator, Solution finder, Competence or capital provider, Market builder, Project champion, Negotiator,* and *Broker.*

For the purposes of this book, the number of people that can be said to have played key roles in the development of the nine products are 31. Some of them have played more than one role in the development of a particular product, and some have also been actively involved in the development processes of several of the nine products. There are of course more people that have been involved in the development processes, but for my approach, which is illustrative rather than exhaustive, the selected number of people is sufficient. The roles of these 31 persons are indicated in the table on next page.
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*Roles played by 31 key persons in the development of 9 selected products*
The people behind Healon

Thirteen people have been identified who, in different ways, contributed to Healon’s successful development. One is, of course, Endre Balazs, primarily in his role as inventor of the technology behind Healon, and as a negotiator. His negotiation skills led to the licensing agreement for Healon of January 1976, which he successfully renegotiated in 1992.

Another key person at an early stage of the development process was Professor Torvard Laurent, who acted as a broker or “door-opener” for Balazs and Healon in relation to Pharmacia. Once, when discussing Healon with a group of students, I was asked: “What would have happened if Laurent had refused to write that letter to Pharmacia’s CEO?” Perhaps the CSO, Harry Hint, had managed to convince his CEO without Laurent’s support, or the project had been offered to another company, or it had never materialized. Who knows?

Many people who worked at Pharmacia in the 1970’s claim that the Healon project would not have survived, had it not been for the above-mentioned Harry Hint. He supported the project when barely anybody else believed in it, he exaggerated its benefits and withheld negative information. Correct or not, he acted the way a project champion, convinced of his or her “baby’s” bright future, frequently does. Another person who took on the project champion role was the project leader, Marianne Granat, until her resignation in March 1976. When talking to Endre Balazs in September 2013, he emphasizes Marianne Granat’s key role in the organization of the know-how transfer between Biotrics and Pharmacia, and in convincing her colleagues of the project’s potential and importance.

Two other persons, without whose contributions the Healon story would most probably have been less fascinating and interesting, are David Miller and Robert Stegmann. Thanks to their innovative way of thinking and their competence within cataract surgery, in combination with Stegmann’s unique possibility of testing Healon on patients in South Africa with advanced cataracts in both eyes, Pharmacia became aware of Healon’s opportunities within ophthalmology.

Gunnar Vikström, my successor as product manager of Healon, was the first, or at least one of the first, to realize the possibility of registering the product as a device instead of a pharmaceutical. By arriving at this solution, the time it took for Healon to reach the market was shortened by an estimated 6-7 years.

When Marianne Granat and Harry Hint had left the scene, Erik Danielsson took over the role as Healon’s project champion at Pharmacia. One of his main tasks was to try to convince Endre Balazs that Pharmacia was the best possible partner for Healon in
spite of the company’s reluctance to enter the osteoarthritis market. Becoming a large shareholder in Biomatrix was a strong symbolic gesture in this context.

Hans Åkerblom, in his role as CEO of Pharmacia Ophthalmics, was instrumental in the development of the marketing strategy that made Healon Pharmacia’s biggest product.

Two other individuals who played important roles in Healon’s success were Bengt Ågerup and Magnus Molitéus. Ågerup was Åkerblom’s closest ally, and was behind many of the creative ideas that contributed to Healon’s success, for example the setting up of a rooster farm. Molitéus, who was the CEO of Pharmacia’s U.S subsidiary, actively supported the implementation of Åkerblom’s marketing strategy on the U.S. market.

During J-E Engkvist’s time as CEO of Pharmacia Ophthalmics, Healon sales grew from 43 to 200 mUS$, a result that qualifies also him for the epithet of “market builder”. Toni Weitzberg acted as Pharmacia’s principal negotiator when the 1976 license agreement with Endre Balazs was re-negotiated in 1992. The most important result of this re-negotiation for Pharmacia Ophthalmics was that they removed themselves from a costly and time-consuming controversy that had been going on for a long time, and could instead concentrate on doing business, at least for a while, as it would turn out.

The people behind Synvisc

The lead role in the Synvisc saga is played by Endre Balazs. He was the original inventor of Healon, and also the inventor of the hylan G-F 20 on which Synvisc was based. In addition to this he was the project champion, and the successful entrepreneur who, together with his wife, Janet Denlinger, established the company Biomatrix. The main reason for starting Biomatrix was to enable the development and launch of Synvisc, thereby proving that Pharmacia was wrong in not trying to introduce Healon in the osteoarthritis market.

Other important roles in relation to Synvisc were played by Janet Denlinger, André Balazs, Bengt Ågerup, Rory Riggs, John Feilders and Johann Scheidt.

Janet Denlinger acted in the entrepreneurial role as a co-founder of Biomatrix. She was also a provider of competence, initially as a product developer, later as a leading executive in a fast-growing, high-tech company. Her product development efforts resulted in products for the cosmetics industry, which generated important income for Biomatrix while Synvisc was still in an early development phase. Her managerial skills were developed through “learning-by-doing” as the company grew from fewer than 50
to more than 400 employees in less than ten years. She was, among other things, responsible for the company’s HR functions, and in charge of its editorial office.

André Balazs, Endre’s son, was actively involved in the development of Biomatrix during the company’s first decade. He designed the company’s original marketing plan, said to have functioned as a platform for Biomatrix’ marketing strategy throughout the company’s existence. He was also responsible for contacts with the financial community, and was instrumental in raising the capital needed for Biomatrix’ expansion and for taking Synvisc from the lab to the market. André’s early experiences from working in an entrepreneurial environment such as Biomatrix’ have served him well in his later career, which has made him one of the most successful entrepreneurs in the global hotelier business.

Bengt Ågerup’s main contribution to Synvisc was the creation of Up-Will Investor KB (see Chapter 14). The capital raised through this company enabled the completion of ongoing clinical trials, which saved valuable time in the launching of Synvisc on the European market.

Rory Riggs, who became board member of Biomatrix in 1990 and was appointed President of the company in 1996, brought with him long experience and excellent competence in international business and financial management. This competence was of great value in the transition of Biomatrix from an R&D company to a fully integrated global biomedical company.

John Feilders was involved in the start-up of Biomatrix’ manufacturing facility in Québec and the early launch of Synvisc on the Canadian market in 1992, and in the development and implementation of the marketing strategy for Synvisc on the European market.

Finaly, Johann Scheidt sped up the process of getting CE certification for Synvisc, as well as Hylaform, by identifying German expertise with unique knowledge about the functioning of the EU system, particularly the EU Medical Devices Directive.

The people behind Hylaform

The roles of Endre Balazs, Janet Denlinger and Johann Scheidt were basically the same for Hylaform as for Synvisc. Bengt Ågerup also had a role in the development of Hylaform, although in a detrimental rather than supportive manner. This refers to the fact the he, while involved in the launching of Hylaform in Europe in his role as CEO of Biomatrix Svenska AB, prepared for, and carried out the launch of a competing product in his role as CEO of Q-Med. Another difference between Synvisc and Hylaform, to the latter’s disadvantage, was the absence of a product champion. Since
no one at Biomatrix had enough time or resources to devote to Hylaform, the product was licensed to Collagen Inc., which soon after was acquired by Inamed. But there was no one in these companies prepared to struggle for Hylaform.

The people behind Restylane

Three people behind Restylane’s successful introduction on the European and U.S. markets are Bengt Ågerup, his wife Helen Ågerup, and Jonah Schacknai, the CEO of Medicis, Q-Med’s licensee for Restylane as well as Perlane on the U.S. market. With Restylane, Bengt Ågerup makes his debut in the role as innovator, after previously having acted as an imitator in the case of Microvisc and Viscorneal. This is a development path for future research on innovation processes to look at more closely: a person starting his or her career in R&D and product development at a major company, who later starts business by imitating the product and production technology of his or her former employer, and who finally, thanks to the learning process he or she has experienced, comes up with something innovatively new. In addition to being the innovator behind Restylane, Bengt Ågerup also acted in the roles of entrepreneur and project champion.

Bengt Ågerup’s wife Helen participated in the launching of Restylane in France by doing marketing in a home-made, unconventional way, which turned out to be very successful. Jonah Schacknai, founder and CEO of Medicis was instrumental in building Restylane’s position as the biggest dermal filler on the U.S. market, a position which later was taken over by Juvéderm.

The people behind Microvisc

Microvisc was the principal product of Bohus BioTech AB, a company started by two entrepreneurs with the support of two risk capitalists. The idea on which Bohus BioTech was built involved imitating a very successful product, Healon, with which three of the four company founders had worked at their previous employer, Pharmacia. In addition to Bengt Ågerup and Daniel Ogbonnaya acting as entrepreneurs, Hans Åkerblom and Göran Ågerup provided capital, and all four of them acted as imitators. Göran Ågerup also acted in the role as solution finder. This was the result of the company’s 1993 liquidity crisis. The crisis was solved by Göran Ågerup lending the capital needed to complete all on going preparatory projects.
The people behind Viscorneal

In the case of Viscorneal, Bengt Ågerup reappears in the role as imitator, this time together with Corneal’s founder, Waldemar Kita, and the company’s research director, Gilles Bos. Ågerup can also be said to have played the role of provider both of technology know-how and raw material in the form of rooster combs. Waldemar Kita acts in the role of entrepreneur, eager to increase his company’s competitiveness on the cataract surgery market by being able to offer eye surgeons a complete package including IOLs (intraocular lenses) as well as an OVD (ophthalmic viscosurgical device). Gilles Bos becomes the project champion by gradually making himself and his team independent of Bengt Ågerup’s know-how.

The people behind Juvéderm

Juvéderm is the next step in Corneal’s conquest of the hyaluronic acid market. This time without Beng Ågerup’s support, and without his knowing, until Juvéderm is launched on the European market in year 2000. The creation of Juvéderm was possible thanks to Gilles Bos’, the research director at Corneal, advancement from imitator to innovator, albeit of an incremental rather than a radical kind. The knowledge gained through his cooperation with Bengt Ågerup concerned only technology related to rooster comb-based hyaluronic acid. The learning process that resulted in the patented Hylacross technology on which Juvéderm is based, included systematization of unstructured, “slip of the tongue” type information from Bengt Ågerup, studies of various patent documents, and creative thinking both by Gilles Bos and his co-workers at Corneal. Waldemar Kita continued in his entrepreneurial role, as principal owner of a fast-growing company, and can also be characterized as the project champion, at least from a business-related perspective.

The people behind Esthélis/Belotero

Esthélis/Belotero became the next stop on Gilles Bos’ learning voyage in the world of hyaluronic acid. In the new company Anteis, where he acted in the role as entrepreneur together with his wife Sylvia Scherer and three former colleagues at Corneal, his innovative ambitions were crowned with the patented manufacturing technology CPM (Cohesive Polydensified Matrix). Based on this technology Anteis was able to launch Esthélis/Belotero, one of the main contenders for Juvéderm and Restylane on the global dermal filler markets.
The people behind Xalatan

In the Xalatan case, for the second time in this book, a person honored with the title of inventor appears. The person is László Bitó, inventor of the prostaglandin patent which eventually led to the development of the anti-glaucoma, blockbuster product Xalatan. But there were many other people involved in the process of transforming Bitó’s revolutionary discovery into a successful product. One person who played a very important role, without spending much time or effort, was Endre Balazs in his role as a broker, or intermediary between Bitó/Columbia University and Pharmacia. Another important role was played by Bengt Ågerup, who saw potential in the prostaglandin project that not many others realized.

Johan Stjernschantz and Bahram Resul were the innovators who transformed Bitó’s patent into a usable product. Stjernschantz also took on the role as project champion and saw to it that the prostaglandin/latanoprost project was supplied with the required resources. His internal counterpart in these negotiations was Pharmacia Ophthalmics CEO, Jan-Erik Engkvist, who made his contribution to the project by giving Stjernschantz the resources he requested. Göran Ando, Executive Vice President of Pharmacia AB and Pharmacia & Upjohn, with valuable previous experiences from Pfizer, Astra and Bristol-Myers, played an important role in the process of Xalatan’s approval by FDA. László Bitó’s colleague Carl Camras was deeply involved in the development process of Xalatan, as well as in the presentation of the product to the global society of glaucoma specialists. Lena Kajland-Wilén and her colleagues at the marketing department were responsible for the strategic market plan behind Xalatan’s successful launching on the global glaucoma market.

To summarize the importance of “P” as in “People” for the successful outcome of innovation processes: Judging from the nine examples selected from The Magic Molecule, it can be said to be a combination of unique solo performances of a recurring or non-recurring nature, in combination with well-orchestrated team efforts.

Permission

There are few products for which official permission, or approval is more crucial, and at the same time more difficult and costly to obtain, than drugs. And there are few governmental institutions which have more power, and are harder to convince than the U.S. Food and Drug Administration, FDA. The discovery in 1979 that Healon could be registered as a medical device rather than a drug was therefore of great importance. To register a medical device with the FDA was considerably less costly and time-consuming than registering a drug, at least at the end of the 1970’s. As seen above
(Chapter 9), it was estimated that Pharmacia’s time gain in the case of Healon was 6-7 years.

To obtain approval from the relevant authority was of key concern already in connection with Pharmacia’s endeavor to launch Healon as a drug for the treatment of arthritis in humans and horses. In those days the responsibility for registration of drugs both for human and veterinarian use laid with the Swedish National Board of Health and Welfare. The fact that Healon had to be registered as a drug was something everybody involved took for granted, and it is doubtful if the alternative to register the product as a device at all existed. The rejection of Pharmacia’s application for the veterinary market in February 1977, due to lack of sufficient clinical data, resulted in the application for the human market being indefinitely postponed. The possibility of getting approval based on the ten clinical trials that had been conducted by that time was considered unlikely.

*Permission and dermal fillers*

The FDA’s 1979 approval of Healon as a medical device in connection with cataract surgery served as a wake-up call: maybe other hyaluronic acid-based products, intended for other uses, could be registered as medical devices? This was further accentuated when the meaning of Council directive 93/42/EEC of 14 June 1993, concerning medical devices, and directive 93/68/EEC, concerning CE Marking began to be realized. This was when, for example, Johann Scheidt met Dr. Wolfgang Müller-Lierheim (see Chapter 15), which led to the EEC-approval of Synvisc and Hylaform.

Of the hyaluronic acid-based products analyzed above, all eight, except Healon, could be launched on the European market from 1995 and onwards thanks to the fact they were approved as medical devices in accordance with Council directive 93/42/EEC and obtained the CE mark.

The competitive advantage of EEC approval and CE marking has been drastically reduced over the last 6-7 years, particularly with regard to dermal fillers. For example, as reported above, in March 2012 no fewer than 110 dermal fillers on the French market were approved by the French Healthcare Safety Product Agency. FDA approval, on the other hand, creates an outstanding competitive advantage for a producer of dermal fillers, not only on the U.S. market, but the entire global market, since it is so difficult to obtain.
During the period December 2003-September 2014 the FDA had, according to their website\(^\text{46}\), approved no more than seven different brands of hyaluronic acid-based dermal fillers, five of which are still on the market. In the case of Restylane and Juvéderm, five and two different versions, respectively, have been approved. With only five brands competing on a market that represents more than half the global market, the value of obtaining FDA’s approval cannot be overestimated.

**Permission and Xalatan**

The Xalatan case also illustrates the crucial importance of obtaining FDA approval, even if the first permission, granted in June 1996, allowed the product to be used only as a secondary treatment option. Many of the members of Pharmacia’s Xalatan team have testified to the meticulous preparation and the enormous tension that preceded FDA hearings in December 1995, and the great relief experienced when approval was finally received. From this it can be concluded that the success of a pharmaceutical or a medical device is as dependent on an organization’s ability to make its way through the approval bureaucracy as on its ability to conduct top level R&D.

**Possession**

“P”, as in Possession, has to do with who possesses the right to decide about a product; when and where to sell it, for what uses, at what price, etc. This right is normally linked to the ownership of a product, but it can also be obtained by acquiring a license. Pharmacia’s control over Healon, which was obtained through the 1976 license agreement (see Chapter 5), prevented Endre Balazs from exploiting the product’s potential on the osteoarthritis market. It was not until Balazs and his research team at Biomatrix had managed to develop new types of hyaluronic acid (hylan A, hylan B and hylan G-F 20), which were not covered by the license agreement, that he could prove he was right in his assumptions.

The Healon case is also an illustration of how change of ownership can influence a product’s development. As long as Pharmacia was in full control of the Healon license, the product’s flagship position within the company was undisputed. Pharmacia’s merger with Kabi in 1990, through which Healon lost its position as the company’s largest product, followed by the Pharmacia & Upjohn merger in 1995, resulted in a shift in product focus to Healon’s disadvantage. The owner’s diminishing interest in

\(^{46}\) [www.fda.gov: Dermal Fillers Approved by the Center for Devices and Radiological Health](www.fda.gov)
the cataract market was finally confirmed in 2004 when Pfizer, shortly after the acquisition of Pharmacia Corp., sold its surgical ophthalmology business, including Healon, to AMO (Advanced Medical Optics Inc.).

Endre Balazs’ negative experiences from the license agreement with Pharmacia with respect to his lack of control of the osteoarthritis market, are reflected in the marketing strategy he and his colleagues at Biomatrix developed for Synvisc. Instead of entrusting the fate of Synvisc to a single company, leading pharmaceutical companies were invited to compete for distribution rights in specific countries or regional markets. This resulted in considerable up-front and milestone payments that increased Biomatrix value on the New York Stock Exchange, which in turn helped to attract interest from potential acquirers of the entire company.

Genzyme’s acquisition of Biomatrix had negative consequences. With regard to Synvisc, they were temporary in nature. In the case of Hylaform, however, the ownership change meant, more or less, that the product received its death blow.

Both Q-Med/Restylane and Corneal/Juvéderm are examples of how change in possession can create a win/win situation. In the case of Q-Med, responsibility for the marketing of Restylane, and later also Perlane, on the U.S. market was transferred to the U.S. company Medicis through a license agreement. From an outside perspective this seems to have been a very advantageous decision for both parties. Medicis had a sales organization capable of taking advantage of Restylane’s potential on the U.S. dermal filler market, and Q-Med could use the resources generated by its U.S. licensee to expand its operations on the European and other markets.

Allergan’s acquisition of the relatively small French company Corneal provided Juvéderm with the necessary resources to challenge Restylane in the battle for the U.S. dermal filler market. The founder of Corneal, Waldemar Kita, on the other hand, got the resources needed to realize his dream, which was to acquire one of the top teams of French football.

Xalatan, finally, can be seen as a successful change of possession from a business perspective, which had negative consequences from a local (the city of Uppsala), regional (the Stockholm-Uppsala Life Science Region) and national (Sweden) perspective. Through Pfizer’s acquisition of Pharmacia Corp., which made many of the wealthy stockholders of Pharmacia even wealthier, a blockbuster in the making disappeared from Sweden, a country once upon a time famous for its internationally successful pharmaceutical industry, and almost nothing was left behind.
Appendix A: The origins of the book and the facts on which it is based

The Magic Molecule has been produced by Svensson & Svensson AB, a consulting firm owned and run by my wife, Anette Clefberg, and myself.

The book’s origin is closely linked to my own role, first as product manager for Healon, and shortly after in evaluating the turn of events surrounding Healon’s initial development during the onset of my academic career. I have since turned my findings into a business case used in my academic teaching. The case has been of significant interest to my students throughout the years, leading me to revise and supplement it from time to time. Such revision has often occurred as hyaluronic acid has been introduced to new markets, or been used for new applications, thus creating a number of new products and new companies.

The story of Healon has followed me throughout my international career within consulting, and as a visiting researcher and diplomat within the UN system. Since my field of expertise has been technology transfer, the Healon case has often been useful to refer to. Consequently I have used the case in connection with presentations and assignments in countries as dispersed as Norway, Chile, Bolivia, Colombia, Nicaragua, Turkey, Austria, Spain, France, India, Australia, Moldova, Oman and Macedonia. During the past 12-15 years I have used the case in my role as visiting professor in business administration at the Swedish University of Agricultural Sciences in Uppsala, Sweden and guest lecturer at the School of Entrepreneurship at Uppsala University.

A couple of years ago I realized that I had gathered enough information about Healon and hyaluronic acid to write a book on the subject. The title of the book was decided the day of my revelation; The Magic Molecule.

Work on the book began during the spring of 2012. Since then I have spent many of my waking hours with The Magic Molecule. It’s a decision I do not regret, and I have found myself continually fascinated and still learning more. The book itself is the result of three main types of information collection:

1. Studies of official documents of companies involved, including annual reports. In the case of the larger companies (Pharmacia, Kabi Pharmacia, Pharmacia & Upjohn, among others) access to documents has mainly been obtained at the Royal Library in Stockholm, and via the Internet. As for the smaller companies described in the book, information has been obtained either from the companies themselves or from The Swedish Companies Registration Office (Bolagsverket).
2. Studies of company specific documentation. The access I once had with regard to the Healon project’s first six years give me an ability to describe precisely the events of the period. Such information has later been appended as a result of unlimited access to the archives of Endre Balazs and Biomatrix, the company started by Balazs and his wife Janet Denlinger in 1981. The documentation includes Balazs’ collaboration with Pharmacia during 1971-1996. It also includes Biomatrix’ documentation in relationship to Bengt Ågerup during 1984-1999. Ågerup was CEO for Biomatrix’ Swedish subsidiary Biomatrix Svenska AB, from 1987 until 1997. I have also had access to company specific documentation from other companies that have been involved in hyaluronic acid-based products in different capacities.

3. Lastly, I have conducted more than 60 interviews in Sweden, the USA, Switzerland, France, Hungary and Germany with individuals involved in the development, production and/or marketing of hyaluronic acid-based and related products. With a few exceptions, people have been very cooperative and endeavored to provide me with as complete and correct information as possible.
Appendix B: References

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Valeant Pharmaceuticals International, Inc., 2010-2013
Appendix C: History timeline of the Magic Molecule

1934: Hyaluronic acid discovered by Karl Meyer and John Palmer at the Biochemical Laboratory of the Department of Ophthalmology, Columbia University
1947: Endre Balazs invited to be a visiting researcher at the Department of Experimental Histology at Karolinska Institutet (KI), Stockholm, Sweden. Among his students: Torvard Laurent, later to become one of the leading Swedish researchers within biochemistry and microbiology, and Harry Hint, later to become Chief Scientific Officer at the Swedish pharmaceutical company Pharmacia AB
1951: Endre Balazs leaves KI (Dec. 1950) and becomes Director of Research at the Retina Foundation, Boston
1965: Endre Balazs becomes Director of the Boston Biomedical Research Institute
1968: Endre Balazs starts Biotrics, Inc. for the commercialization of his research results concerning hyaluronic acid
1971: Endre Balazs meets Torvard Laurent and Harry Hint in Uppsala. The meeting results in that Pharmacia is offered the licensing rights for Healon®
1972: Option to license agreement (OLA) signed between Pharmacia and Biotrics in September. The OLA is extended twice: September 1973 and April 1974
1974: License agreement, not including North America, signed in October 1974
1975: Endre Balazs joins the Eye Institute at Columbia University, gets the Malcolm P. Aldrich chair
1976: Final, world-wide license agreement signed between Pharmacia and Biotrics, Inc. in January.
1976: Healonid® Vet. launched on the French veterinary market in October
1977: Pharmacia’s application for Healon (Hylartil®) on the Swedish veterinary market not approved. Application for the human market is postponed
1977/78: David Miller and Robert Stegmann discover Healon’s usefulness in connection with cataract operations
1978/79: Pharmacia realizes that Healon can be registered as a surgical device for ophthalmic surgery without further clinical trials. 510(k) authorization to market Healon is received from FDA in the autumn of 1979.
1980: - Healon is launched on the U.S. market (April)
- Pharmacia Ophthalmics is established (August)
1981: Biomatrix, Inc. is created by Endre Balazs and Janet Denlinger
1982: - Columbia University and László Bitó get approval for the prostaglandin patent (the ‘353 patent
- Pharmacia Ophthalmics buys Medical Workshop B.V., Dutch producer of IOL’s (intraocular lenses)
- The first cosmetic products based on ingredients supplied by Biomatrix are launched on the market, including Estée Lauder’s Night Repair®
1983: - Pharmacia Ophth. acquires the ‘353 patent from Columbia Univ. and László Bitó
- Jan-Erik Engkvist new CEO of Pharmacia Ophthalmics
- Healon becomes Pharmacia’s biggest product
- Biomatrix announces the discovery of the hylan B gel
1984: - Erik Danielsson new CEO of Pharmacia
- Bengt Ågerup leaves Pharmacia and signs consulting agreement with Biomatrix
- Biomatrix announces the discovery of hylan A
1985-87: Pharmacia acquires 8.1 percent of Biomatrix for 4.19 mUS$. The second acquisition is made on October 19, 1987: “Black Monday”

1985:
- Bengt Ågerup starts Q-Med
  - Endre Balazs retires from Columbia University, starts to work full-time as CEO and CSO of Biomatrix
  - Biomatrix announces the discovery of hylan G-F 20 (Synvisc*)

1986:
- Waldemar Kita starts Corneal, French company producing IOL’s
  - Pharmacia Ophthalmics buys Intermedics Intraocular, Inc. in California
  - Healon launched on the Japanese market
  - Johan Stjernschantz is employed at Pharmacia Ophthalmics and becomes project manager for the prostaglandin project

1987:
- Biomatrix, Inc. starts subsidiary in Sweden: Biomatrix Svenska AB, and appoints Bengt Ågerup as CEO
  - Drs. Jean and Alastair Carruthers discover the cosmetic properties of botulinum toxin (Botox)

1988:
- Pharmacia balks at additional investments in Biomatrix

1990:
- Kabi and Pharmacia merge.
  - Erik Danielsson quits as CEO of Pharmacia
  - Jan-Erik Engkvist quits as CEO of Pharmacia Ophthalmics
  - Toni Weitzberg new CEO of Pharmacia Ophthalmics
  - Up-Will Investor KB created on Bengt Ågerup’s initiative, to finance clinical trials for Synvisc in Europe
  - Bengt Ågerup initiates discussions with Daniel Ogbonnaya, Hans Åkerblom and Göran Ågerup which lead to the start of Bohus BioTech two years later

1991:
- Biomatrix listed on NASDAQ
  - Bengt Ågerup, in his role as CEO of Biomatrix Svenska AB, starts co-operating with Johannes Reinmüller and Hans Schwall

1992:
- The 1976 license agreement between Endre Balazs (Biotrics) and Kabi-Pharmacia is renegotiated
  - Filing of the Latanoprost patent (Stjernschantz and Resul)
  - Bohus BioTech starts its operations in Strömstad, Sweden
  - Bengt Ågerup starts transferring know-how to Corneal on how to produce rooster comb-based hyaluronic acid
  - Johannes Reinmüller and Bengt Ågerup participate in the annual conference of the German association for aesthetic medicine in Lindau
  - Letter of intent signed between Bengt Ågerup (Biomatrix Svenska AB), Reinmüller and Schwall concerning distribution of Hylaform in Germany
  - Synvisc launched in Canada

1993:
- Canadian incident: Microvisc Plus, produced by Q-Med, causes eye infections among 14 patients in Montreal
  - Letter of intent between Biomatrix, Inc., Kilfo Gmbh and Daedalus concerning Hylaform in Germany
  - Bohus BioTech suffers from strained liquidity. Saved by loan from Göran Ågerup
  - Biomatrix signs license agreement with Syntex Pharmaceutical for eight European countries

1994:
- Bohus BioTech is reorganized after the Canadian incident and revelation of Bengt Ågerup’s co-operation with Corneal. Bengt Ågerup and Hans Åkerblom leave the company, Göran Ågerup and Daniel Ogbonnaya remain
  - Granting of the Latanoprost patent
  - Bengt Ågerup’s co-operation with Corneal ends
Johannes Reinmüller conducts a clinical trial for Q-Plast (pilot version of Restylane) on behalf of Q-Med

1995:
- Biomatrix obtains CE-mark for Synvisc and Hylaform
- Synvisc launched by Hoffman-La Roche in Sweden
- Q-Med files the NASHA patent application
- Daedalus Gmbh and Brixton Medical AB sign distribution agreement concerning Restylane
- Biomatrix signs distribution agreement with Collagen Inc. concerning Hylaform
- Kabi-Pharmacia merges with Upjohn, which results in Pharmacia & Upjohn
- FDA-hearing on Xalatan (December)

1996:
- FDA approves Xalatan as a second-line therapy (June)
- Xalatan is launched on the global market.
- Settlement of dispute between Endre Balazs and Pharmacia & Upjohn concerning royalty payments for Healon
- Bengt Ågerup terminates co-operation with Daedalus Gmbh
- Collagen Inc. launches Hylaform on the European market
- Q-Med obtains CE-mark for Restylane and launches the product shortly after Collagen’s launch of Hylaform
- Distribution agreements for Synvisc signed with leading pharmaceutical companies in different parts of the world

1997:
- Bengt Ågerup quits as CEO of Biomatrix Svenska AB
- Marketing agreements for Synvisc with multinational drug companies give Biomatrix over 100 mUS$ in upfront fees and milestone payments
- Xalatan sales the first full year on the market amount to 165 mUS$

1998:
- Biomatrix listed on the New York Stock Exchange
- Xalatan has climbed to become Pharmacia & Upjohn’s second biggest product
- László Bitó launches his book “Abraham and Isaac”

1999:
- Settlement reached in lawsuit where Biomatrix has sued Q-Med for patent infringement
- Q-Med is listed on the Swedish stock exchange

2000:
- Corneal obtains CE-mark for Juvéderm
- Genzyme Corp. acquires Biomatrix
- Pharmacia & Upjohn is merged with Monsanto and Searle, which results in Pharmacia Corp.

2002:
- Allergan obtains FDA-approval for Botox Cosmetic
- Xalatan approved by FDA as first-line therapy

2003:
- Q-Med obtains FDA-approval for Restylane
- Q-Med signs license agreement with Medicis for Restylane and Perlane on the North American market
- Gilles Bos and Silvia Scherer together with three former colleagues at Corneal start Anteis in Geneva
- Pfizer’s acquisition of Pharmacia Corp. is completed

2004:
- Hylaform approved by FDA
- Pfizer sells its ophthalmics division, including Healon, to AMO (Advanced Medical Optics)

2006:
- Juvéderm approved by FDA
- Allergan buys Corneal, including Juvéderm

2008:
- Genzyme Corp launches Synvisc-One in Europe

2009:
- Abbot Laboratories acquires AMO including Healon
2011: - Belotero Balance, produced by Anteis and sold by Merz on the U.S. market, approved by FDA
  - Juvéderm, according to Allergan, has captured position as the world’s No.1 selling dermal filler brand
  - Swiss Galderma buys Q-Med for 1.22 billion US$
  - Sanofi buys Genzyme Corp.
2012: - Valeant buys Medicis
2013: - Anteis acquired by Merz
2014: - Galderma reclaims U.S. sales rights for various products, incl. Restylane and Perlane from Valeant
  - Actavis plc. acquires Allergan, incl. Juvéderm, for 66 billion US$
2015: Production of Healon continues at Fyrislund, Uppsala, based on hyaluronic acid from rooster-combs. Healon is estimated to be used in 8.000 cataract operations every day.
Appendix D: Acknowledgements

The Magic Molecule has benefited from support and wise comments from many individuals. Anette Clefberg, my wife and business partner, has been involved in the project from day one as a speaking partner and critical reader of my drafts. Others who have given me constructive criticism and feedback are our children Lisa Clefberg Liberman, Kajsa Nylander and Martin Svensson Henning. Some of my best friends, who in some cases also are current or former colleagues, have read the manuscript at different stages of development and provided valuable comments and insights: Göran Lindström, Leif Nilsson, Christer Olofsson, and Christer Wandér. Erik Sandewall gave me valuable advice on publishing matters, and Dustin Swepston has made the book accessible to an international audience by either translating my Swedish, or correcting and improving my English.

I also want to express my gratitude to some people who, unconditionally, have given me access to unique documentation of exceptional value for the writing of this book. In one case I am referring to a decision that was made long time ago – at the beginning of 1977 – by, among others, Pharmacia’s (at that time called Fortia) then CEO Gösta Virding, which gave me access to all existing documentation for the first six years of the Healon project. This documentation forms the basis of Part I of my book.

Another decision, made by Endre Balazs and Janet Denlinger in November 2012, resulted in access to all existing documentation concerning Endre Balazs’ and his company Biotrics’ dealings with Pharmacia during more than 25 years, and the complete files of Biomatrix, Inc. The Balazs’, Biotrics’- and Biomatrix’-files provide important input to the book’s Part II, III and V.

I have also been provided with unique documents by László Bitó, the inventor of patent ‘353, which have been used in the writing of Part IV, which is about Xalatan, the blockbuster drug for the treatment of glaucoma.

Finally, I want to thank all the interviewees, in total more than 60, who, by sharing their memories and experiences, have made the writing of this book such a fascinating and exciting journey.
Appendix E: About the author

(Photo: Kajsa Nylander)

Börje Svensson was the first product manager for Healon at Pharmacia (1975-76). He has a Ph.D. in business administration from Linköping University, Sweden and has specialized in the transfer of technology and knowledge between different environments. He has extensive international experience, has held senior managerial positions within academia, industry and the U.N. system, and has been a board member of organizations, both in the private and public sector, working with innovation and entrepreneurship.

His experiences include three years as an industry development consultant and visiting researcher in Chile and Bolivia in the early 1990’s, Vice President of Linköping University, Sweden, responsible for matters related to innovation and entrepreneurship (1994-1996), Director of the Industrial Policies and Research Branch at United Nations’ Development Organization (UNIDO) in Vienna (1996-1998), board member of Karolinska Institutet Holding AB (2006-2008), and CEO of Karolinska Institutet Health Management AB (2008-2012). He has also been an adjunct and visiting professor in business administration at the Swedish University of Agricultural Sciences in Uppsala, Sweden (1999-2008).

Börje Svensson is currently president of the consulting firm Svensson & Svensson AB, president of the male-voice choir Stockholms-OD, and president of the Industrial Fund of the Swedish-French Research Association (AFSR).