100 years of pioneering allergy solutions

Kurt Jacobsen

Kurt Jacobsen, Professor, dr. phil.,
Centre for Business History,
Copenhagen Business School (CBS)

Prologue

As well as the stated sources and references in the notes, the first four chapters are based on interviews with Elsebeth Budolfsen, Dorde Venov, Henning Løwenstein, Suzanne Gravesen and Lars Jacobsen. In addition to this, a roundtable discussion was held with Jens Bager, Torbjørn Bjerke, Erik Sørensen and Henrik Jacobi, as well as a discussion with Domingo Barber and Carlos Cortés. Finally, the manuscript has been regularly discussed in detail with Jacob Frische.

Apart from the sources and references cited in the notes, the last five chapters are based on interviews with Anders Hedegaard, Carsten Hellmann, Henrik Jacobi, Søren Jelert, Søren Niegel, Christian Houghton, Lene Skole, Lisbeth Kirk, Leif Høy and Lars Blume Schackinger. There was also a round-table meeting with all of the senior management of ALK, and I have had regular discussions with Jeppe Ilkjær and Per Plotnikof.

Thanks to all of them.

Kurt Jacobsen, 29 March 2023.

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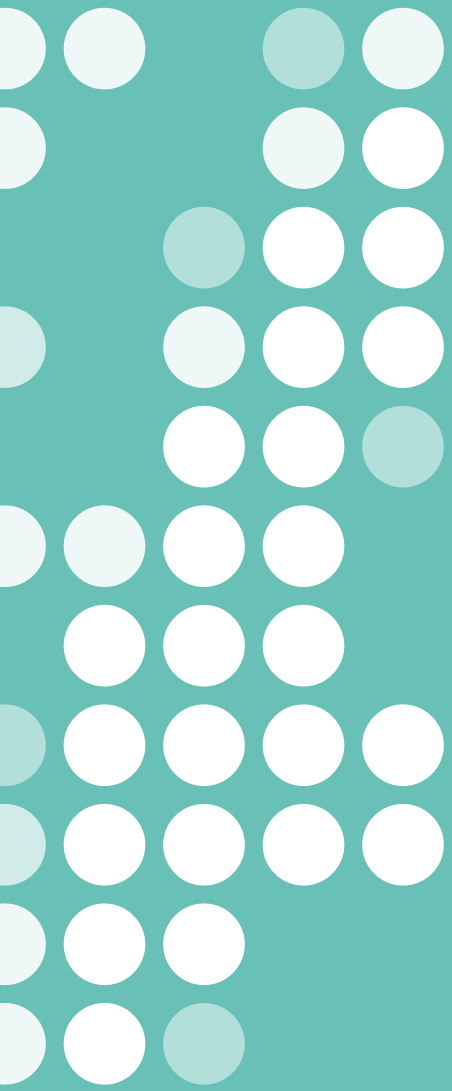


1.

The early days

A Danish doctor comes home

In March 1921 a young doctor, Kaj Hedemann Baagøe, returned to his native Denmark after a six-month sojourn in the USA. With him, he brought preparations for inducing cutaneous reactions – allergic reactions that make the skin swollen or inflamed and itchy – together with a recipe for preparing similar preparations.

Not long after his return, Baagøe took up an appointment as a clinical assistant in the laboratory of the paediatric department at the Rigshospital (Copenhagen University Hospital). Here, he approached his superior, Consultant Professor C.E. Bloch, for permission to prepare and test preparations based on the American formula.

Bloch was somewhat disapproving, and it is possible that he objected to the idea of deliberately irritating the skin to produce allergic reactions. He was not wholly negative about the idea, however, and sought advice from his colleague Professor Knud Faber, a leading Danish medical expert, whose response was less than enthusiastic.

As Baagøe later put it: 'Professor Faber took the view that this business of scratching people with things like roast chicken was mere American bluffing.' Despite these misgivings, Baagøe was granted permission to proceed with his plans, provided he promised to spend his time on 'something sensible' as well.[1]

Baagøe went ahead with his project and within a year had prepared some 90 preparations based on the American recipe. He had also collected a variety of pollens, which he treated with ether to preserve them. When he was appointed to the post of senior registrar in the hospital's paediatric department in November 1922, however, he had to suspend production of his preparations, at least for the time being.

He did not entirely abandon his work on allergies and allergic reactions, though. Early in 1923 he entrusted the production of his preparations to the hospital's pharmacist, Peter Barfod, who continued the work. For his own part, Baagøe began research into asthma in children, particularly in relation to allergy. This was the beginning of an unusual partnership between the two men, which laid the foundations

Kaj Hedemann Baagøe (born in 1888), photographed in 1966.

for the Allergologisk Laboratorium (Allergological Laboratory) and, eventually, the pharmaceutical company ALK.

From the Egypt of the Pharaohs to Copenhagen University Hospital

Kaj Baagøe was born on 5 May 1888 in Næstved, where his father was proprietor of the Løve (Lion) pharmacy. Having left the prestigious Herlufsholm Boarding School with the best possible grades in 1906, Baagøe enrolled in the medical faculty at the University of Copenhagen. He graduated with distinction in 1913 and embarked upon a series of short-term positions as junior doctor and locum in Copen-

hagen hospitals. A number of these were in paediatric departments, including one at the Queen Louise Children's Hospital and, in 1919, Baagøe travelled to Stockholm and Berlin to study children's diseases.

Times were hard, however, and it was difficult for young doctors to find permanent positions. Deciding to try his luck on the other side of the Atlantic, Baagøe headed for the USA in autumn 1920. He had received an offer of a permanent position in a Chicago hospital, but there was some kind of misunderstanding and the job failed to materialise. He was quickly offered a job in the Columbus Laboratories in Chicago instead, where he began work in September. In this post he forged contacts with the Children's Memorial Hospital, where he first encountered the subject of allergic cutaneous reactions.

When he set off on his return trip to Denmark in March 1921, Baagøe's route took him through Boston, where he paid a visit to the American professor Chandler I Walker, the leading allergy expert in the USA.

Walker was a consultant at the Peter Bent Brighams Hospital, which was associated with Harvard Medical School. He demonstrated a positive cutaneous reaction for Baagøe, and it was enough to awaken an intense interest in the young Danish doctor.

Allergic reactions had been known since the days of the Egyptian Pharoahs and ancient Greece. In the 16th century, the Italian doctor Leonardo Botallo described an illness he called 'rose fever', in which patients displayed asthmatic symptoms after plucking roses. The first skin test was carried out in 1869 by an Englishman, Charles Blakeley, who put pollen into a cut in his own skin in order to provoke an allergic reaction.

The term 'allergy' had first been used in 1906, by the Austrian paediatrician Clemens von Pirquet, to describe this type of over-sensitivity that was not the result of any known illness but was thought to be induced by external influences on otherwise healthy individuals.

A further breakthrough in terms of treatment had come in 1911-14, when Leonard Noon and John Freeman helped lay the foundations of the treatment later known as allergy vaccination, desensitisation or immunotherapy, where, by injecting patients with increasing doses of allergy-inducing substances, allergic reactions could be prevented or limited.

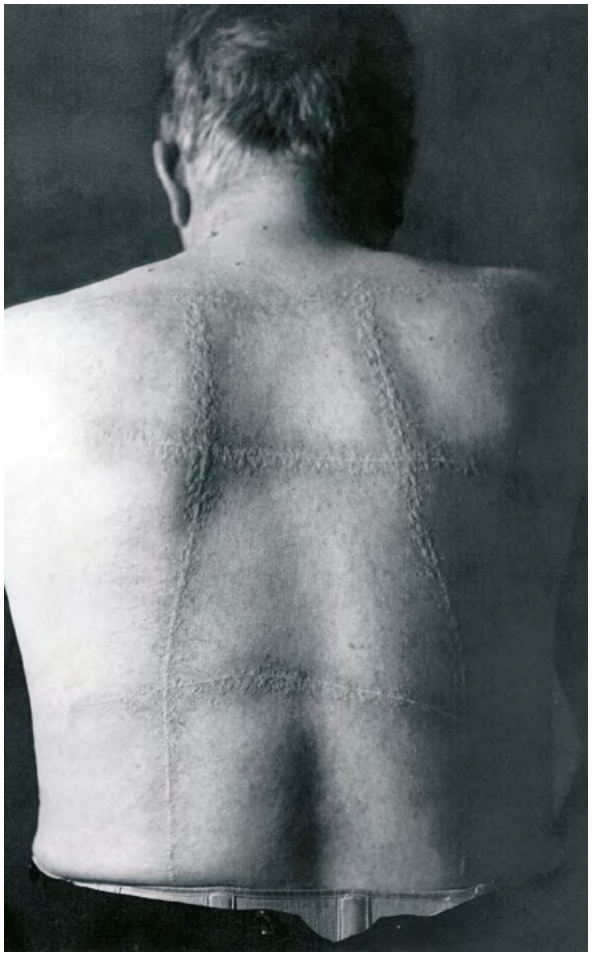
The actual cause of allergic reactions remained a mystery, however, and at the time of Baagøe's trip to the USA, allergology as a medical speciality was still in its infancy. Academic literature on the subject was extremely scarce. The first scientific articles, which had appeared in 1916-17, were mainly by American doctors who believed that allergic reactions were caused by proteins.

On his arrival home in Denmark, Baagøe wrote to his American colleagues to ask for offprints of their articles and used these as the basis for his own work. He also began making preparations under primitive conditions that illustrate just how new the field was. Years later, in a historical retrospective, he described how he had made his first extract of cat hair:[2]

'I asked the hospital porter to get me a cat, and he was lucky enough to be able to trap two fully grown cats which he brought to me in the laboratory one evening. I tipped a large bottle of chloroform into the trap, and when the cats were anaesthetised, I pulled them carefully out and hung them by the tails on the fume cupboard, cut their throats and let them hang there all night. Next day the hair was shaven off and boiled in water for an hour over a low flame. Then the hairs were sieved off and the filtrate was evaporated with a blow dryer. The dried sediment was treated with ether, and the whole dried mass was pulverised in a mortar. The preparation was complete. When compared with the American preparation it proved to be just as good – and I had enough cat hair to last me for years.'

It was hardly surprising that Professors Bloch and Faber had reservations about this sort of production method and perhaps had difficulty in seeing the medical value of cat hair.

Nevertheless, the possibilities were far-reaching. The purpose of making the preparations was to produce an extract that could be used to test patients and determine whether they were allergic to that particular substance. At that time, a typical test involved scoring long, criss-cross incisions into the patient's back and applying an extract – a methodology that doubtless represented another challenge for Professors Bloch and Faber. Later on, more humane methods were employed.



Early experiments with skin reactions at the Copenhagen University Hospital, 1922-24.

The test could be highly beneficial for patients, alerting them to avoid contact with (for example) cats, and thus avoid an allergic reaction to cat hair. The same was true for any substance that was not in itself seen to be a cause of illness; the early allergologists had made the important observation that it was often common, everyday substances that made people ill – substances that were otherwise regarded as totally harmless and part of everyday life.

That was the purpose of the test involving 'roast chicken' about which Knud Faber had made such disparaging remarks. In fact, the American tests would have used an extract, not an actual chicken. Some of the first preparations made by Baagøe and Barfod were produced from such everyday items as fish, chicken, veal, horsemeat, pork, prawns, milk, grain, rice, textiles, hair and feathers. They were used to test patients, both for research purposes and to improve their daily lives.[3]

A more important question, however, was whether the extracts could be used to develop a specific vaccine to prevent allergic reactions. The smallpox vaccination had been developed as far back as the 18th century, and the next obvious step was to apply the same methods and concepts and investigate ways of treating allergies that involved inducing the body to produce its own antibodies to prevent allergic reactions. The doctors of the day had no way of knowing that the body's allergic mechanism works differently to this.

It was one thing to come up with the concept but putting it into practice was a different matter altogether. Research and development were needed. In his new position as a paediatrician, Baagøe began to investigate the link between allergies and asthma, using, among other things, the preparations now being produced by the pharmacist, Barfod.

An unusual collaboration

Peter Christian Kierkegaard Tang Barfod, to give him his full name, was born on 9 October 1876 in Aalborg, where his father, the treasurer of the local diocese, had recently been appointed to the post of hospital superintendent. After graduating as a bachelor with top marks from the Farmaceutiske Højskole (The Pharmaceutical College) in 1898, Barfod worked in pharmacies in Copenhagen, Slagelse and Gothenburg, completed courses in fermentation physiology, applied physics, bacteriology and experimental pathology, and conducted a variety of pharmaceutical studies, the results of which were published in *Archiv for Pharmaci og Chemie (Archive for Pharmacy and Chemistry)*.

On 1 August 1910, Barfod was appointed as the first pharmacist at the new Rigshospital that was being built on Blegdamsvej in Copenhagen. In the space of just two months, he had the pharmacy ready for the hospital's opening on 1 October: 'Never before have we seen a pharmacy fitted out in such a short time,' wrote *Farmaceutisk Tidende (Pharmaceutical Times)*.[4]

After his appointment, Barfod made a number of study trips to hospitals, pharmaceutical companies and laboratories abroad. During the First World War, he oversaw the setting-up and operation of two field hospitals for prisoners of war at Hald and Horserød, which received all their medicines from the Rigshospital pharmacy. He was awarded the Mindetegn for Dansk Krigsfangehjælp 1914-1919 (Danish Red Cross Medal) and several foreign decorations for his efforts.[5]

In many ways, the collaboration between Baagøe and Barfod was a meeting of two quite different worlds – the law stipulated that doctors should not operate pharmacies and chemists should not practise medicine. So Baagøe, the doctor, researched the causes and treatments of illnesses, performed diagnoses and specified the medicines with which to treat the patient. Barfod, the chemist, made and sold the medicines. The two professions were closely linked to the health sector yet, as a rule, there was little collaboration between doctors and chemists. Quite the contrary, in fact; relations between the two professions were cool and characterised by a purely professional cordiality. And, at the very time that Baagøe and Barfod launched their collaboration, this state of affairs erupted into open conflict.

Danish pharmacists had enjoyed a monopoly on the production and sale of medicines since 1672. They were mixed by hand and all pharmacies were permitted to produce them. This arrangement was undermined by the advent of the pharmaceutical-chemical industry, which had developed into a bona fide medicinal industry by the end of the 19th century. The Danish chemists' monopoly on the production of medicines was abolished in 1913. In 1922, the Danish Pharmaceutical Association set up a special 'composition committee', which, supported by a laboratory, undertook the development of standardised medicines for uniform mass production, packaging and labelling. These were to be sold in all Danish pharmacies under the DAK trademark. The idea was to keep the production of medicines in the hands

Peter Barfod (born in 1876), photographed in 1928.

of Danish pharmacies, and prevent the powerful international pharmaceutical industry from taking over completely.[6]

However, the DAK arrangement led to a vehement confrontation between Danish chemists and doctors. It broke out in 1923 after several doctors wrote pieces on 'chemist quackery' in the weekly publication for doctors, *Ugeskrift for Læger (Medical Weekly)*, in which they criticised chemists for not producing medicines of the same high quality and standardisation as the pharmaceutical industry. The chemists hit back in *Farmaceutisk Tidende* and *Archiv for Pharmaci og Chemie*, and the row reached even greater heights as a result of a personal feud between the editor of *Ugeskrift for Læger* and the chairman of the Pharmaceutical Association.[7]

9 June 1923: Barfod's first preparation

It was in the midst of this row that Baagøe and Barfod joined forces to develop preparations to induce cutaneous reactions. It was undoubtedly significant that neither Baagøe, the doctor with a background in a chemist's family, nor Barfod, the chemist with a background in a hospital environment, felt that there was any chasm between them that could not be bridged. Nevertheless, theirs was an unconventional partnership in a turbulent time, driven by a shared interest in alleviating the suffering of allergy patients.

In the USA, Baagøe had witnessed more than the use of extracts to provoke cutaneous reactions. Chandler Walker had been carrying out research into 'vaccinating' asthma patients by injecting them with small, gradually increasing doses of the substance that induced the cutaneous reactions, and Baagøe had also brought notes home with him on the use of extracts in 'prophylactic treatment' by means of injection. This was not designed to cure patients, but rather to treat them in advance and prevent attacks.[8]

Given the number of years he had worked in private pharmacies, Barfod undoubtedly understood the commercial potential of such a method of treatment. (He still worked in two Copenhagen pharmacies in addition to his position at the hospital.)

The collaboration between the two men was also helped by the fact that as a hospital chemist, Barfod was under no pressure from private clients because he only made and supplied medicines for use in the Rigshospital. This allowed him to devote time to research and development. Barfod said himself that he was 'fortunate – because of my position – to be working so closely with the doctors that I was forced to keep up with everything new in the pharmaceutical area'. The hospital management also allocated extra staff to help him start the production of allergy preparations.[9]

Barfod's work soon led to results. In a journal entry for 9 June 1923, he was able to record the first pharmaceutically manufactured allergy preparation in Denmark – a goose-feather extract. Given the level of knowledge at the time, he was not to know that goose and other feathers are not a serious source of allergy but that, in fact, it is the dust mites in duvets and pillows that induce reactions. Nevertheless, a train of thought had been set in motion that led to the production of a whole succession of documented preparations.

The goose-feather extract marked the beginning of actual pharmaceutical production of allergen preparations. As a result, the date of 9 June 1923 marks the establishment of the Allergological Laboratory, and consequently of ALK. The day would next be celebrated on its 40th anniversary in 1963.

'Flogging is not the right treatment'

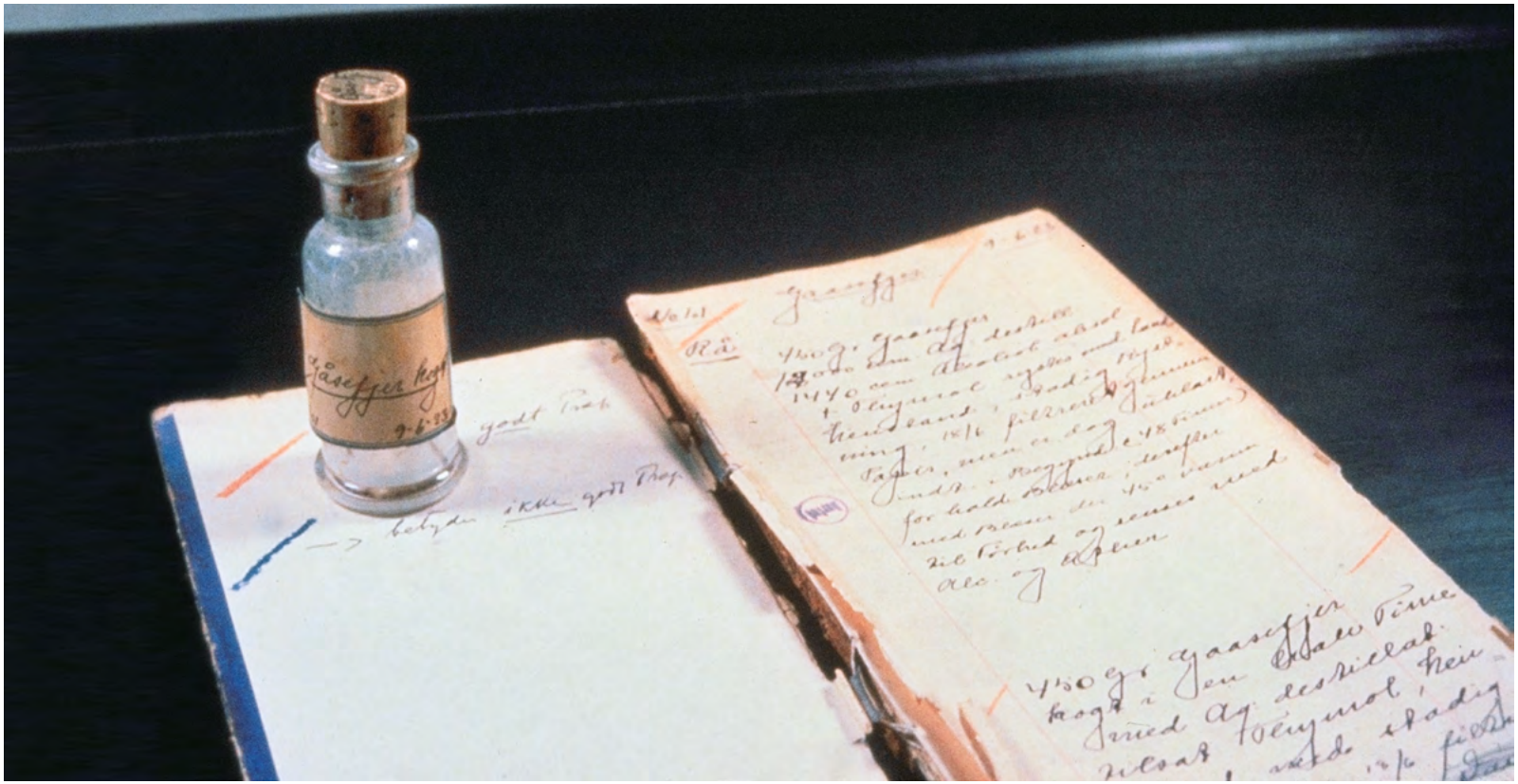
Following his appointment as a senior registrar in the Rigshospital's paediatric department in November 1922, Baagøe launched a research project, in the course of which he examined and tested 124 asthma patients (92 of them children under the age of 16) for cutaneous reactions. In order to compare any differences in effect, he used both imported American preparations and Danish preparations made by himself and Barfod. He used 42 normal, healthy children at a children's home as a control group.[10]

In 1923, Baagøe published his first article in *Ugeskrift for Læger*, and a series of scientific articles soon followed in Danish and international journals until April 1925, when he was made a specialist in paediatrics. In 1926, he published the collected results of his research in the form of a doctoral thesis, which he defended at Copenhagen University on 9 September. The title of the thesis, *Bidrag til Studiet af Asthma særlig hos Børn (Contribution to the Study of Asthma, particularly in Children)*, did not exactly exude excitement and drama, yet it was a pioneering document that detailed the links between allergy and asthma, observing that, for example, asthma patients were often allergic to feathers and needed to avoid them in duvets and pillows.[11]

Until then, the prevailing view among Danish doctors had been that asthma in children was a result of the child being spoiled and attention-seeking. Baagøe has related that Professor Monrad, a consultant at the Queen Louise Children's Hospital in Copenhagen, took the view that a child's 'hysteria' was the result of spoiling by the mother. Consequently, treatment entailed advice to the mother to refuse to pander to the child when an asthmatic attack seemed imminent, and even to leave the room. The best cure for the illness was believed to be a scolding, or worse. In his thesis, however, Baagøe demonstrated that, as he wrote, 'asthma is not a hysterical but an allergic condition, and flogging is not the right treatment'.[12]

As a doctor, Baagøe was lauded for his doctoral thesis, but he made no secret of the fact that he had not worked alone. In his foreword he thanked Barfod for his 'untiring energy and sacrifice' in producing the extracts that had made his research possible.[13] Given the conflict between Danish doctors and chemists at the time, it was

Peter Barfod's first recorded extract of goose feathers, 9 June 1923.



revealing that the doctor and the chemist wrote a joint article for *Hospitalstidende* in which they gave an account of how the extracts were produced. This was followed up in the next issue by an article by Baagøe titled 'Comparative cutaneous tests with Danish and American preparations'.[14]

To Baagøe's disappointment, his thesis generated only 'passing interest', as he described it, among Danish doctors, although he was able to derive some satisfaction from the fact that Knud Faber himself introduced cutaneous tests in his department.

Baagøe received correspondence from all over the rest of the world, including positive reactions from allergologists and others with an interest in the subject, and his results were cited in international journals and textbooks.[15]

In Denmark, however, interest in medical circles remained limited. Baagøe was appointed a senior registrar at Copenhagen County Hospital in November 1926 but, although there was the prospect of his becoming a consultant in due course, he resigned his position in January 1930 and moved to Kolding. There, since he had also become a specialist in internal medicine, he set up as a specialist in children's and medical illnesses.

‘Does baker’s snuffle only afflict the provinces?’

Baagøe did not give up his allergy research, and continued to write scientific articles on the subject too. He began an investigation into bakers, initially in Kolding then extending into the Kolding-Vejle-Fredericia area and showed that many of them contracted head colds and asthma as a consequence of working with flour. The results of the study were published in 1933, in *Den Danske Møller (The Danish Miller)*, published by the Danish flour-milling industry, *Ugeskrift for Læger, Hospitalstidende* and a Scandinavian medical journal. These articles awakened considerable interest far beyond the local area. Newspapers in Copenhagen and Oslo ran interviews with master bakers and factory inspectors who knew nothing of the condition: ‘Does baker’s snuffle only afflict the provinces?’ asked one sceptical headline in *Berlingske Tidende*, while *Norsk Bakertidning (Norwegian Baker's Times)* concluded:[16]

‘It is very good to see that the health authorities in both Denmark and Norway are reacting vigorously to the sensational article by the Danish doctor; this is also the best guarantee that the baking trade is not harmful.’

International allergologists, on the other hand, praised the study. In 1937, Baagøe was invited to lecture on the subject in Lübeck, with a view to publishing in a German allergy textbook. The first edition of the book was published in 1939 and included an edited version of Baagøe’s lecture.[17] In 1938, Denmark became the first country to recognise baker’s asthma as an occupational ailment that warranted being covered by social insurance.

Baagøe never returned to hospital work, instead he continued with his private practice in Kolding. But he carried on publishing articles on allergy subjects – his last article was published in 1975 – and remained a renowned figure in Danish and international allergology. He was recognised as the pioneer of allergology in Denmark and a leading authority in his area, both within medical circles and beyond. Every year, hundreds of allergy patients from across the country sought out his practice in Kolding.

‘… has shown significant proficiency in both practical and scientific areas and has always shown great willingness to place his abilities at the disposal of the pharmacy.’

From Proclamation of Peter Barfod as Knight of the Dannebrog

Production at Frihavn Pharmacy

Baagøe's decision to move to Kolding meant a parting of the ways with Barfod. But the long-time partners kept in personal contact, and Baagøe continued to use allergen preparations produced by Barfod in the diagnosis and treatment of his patients.

Baagøe was not the only one to take up a new job. On 1 October 1928, Barfod finally went into business for himself, taking over Frihavn Pharmacy at Strandboulevarden 61 in Copenhagen, where he continued to produce allergen preparations. The large pharmacy was well-equipped, having already been fitted out with evaporators, percolators for extracting plant juice and presses when it first opened in 1910.[18]

Package insert, Frihavn Pharmacy, 1930s.


Frihavns Apotheket
STRANDBOULEVARD 61.
TELEFON:
CENTR. 1300.

1
Husstøv-Vaccine til antiallergisk Behandling gives som Injectioner under Overhuden.
2
Det er af stor Vigtighed, at intet af det injicerede kommer ind i et Blodkar.
3
Størrelsen af den første Dosis bestemmes efter Udfaldet af Cutan-Prøverne eller Intracutan-Prøverne (R. H.), der foretages med Vaccine i forskellige Concentrationer.
4
Vaccinen kan virke meget forskelligt paa forskellige Patienter. Nogen generel Brugsanvisning kan derfor ikke gives.
5
Ved uhensigtsmæssig Anvendelse er Husstøv-Vaccine et farligt Middel. Det maa derfor fraraades at bruge den uden Kendskab til Litteraturen om Spørgsmaalet.

Shortly before this, on 13 June 1928, Barfod was honoured with the title of Knight of the Dannebrog. The citation stated that, 'in his position at Rigshospital he has shown significant proficiency in both practical and scientific areas and has always shown great willingness to place his abilities at the disposal of the pharmacy'.[19]

While his position in the Rigshospital pharmacy and his collaboration with Baagøe had presented Barfod with excellent opportunities to develop preparations and have them tested on patients, his new venture at Frihavn Pharmacy gave him the opportunity to develop the commercial potential of his extracts. Barfod was the classic chemist who, as the expression went, 'made everything himself', but in addition to the traditional production of medicines, he now began to produce and sell allergen preparations too. Twice a week, two pharmacists from the Rigshospital pharmacy came to fill small bottles with extracts, but otherwise the pharmacy staff developed and produced extracts for sale to doctors and patients both in Denmark and abroad, mainly to specialists and hospitals elsewhere in Scandinavia.[20]

Frihavn Pharmacy's first product catalogue shows that it was able to supply 30 different preparations for cutaneous allergy tests and 21 for subcutaneous tests (injections under the skin). Furthermore, inserts from packaging dating from the 1930s show that Frihavn Pharmacy not only sold preparations for the diagnosis of allergies, but had also developed a method of vaccination in line with Baagøe's notes and experiences from the USA. The method consisted of dissolving dried extracts in sterile water and injecting this under the skin until the patient could tolerate the substance in question. This was preventative in the sense that, if the treatment was started a number of weeks before the pollen season, it would be able to prevent the outbreak of pollen allergy.[21]

Given the limited knowledge of the time, Barfod was not in a position to identify the allergens (proteins), so he was unable to control the level of active substances contained in his preparations, which made precise dosage difficult. As a result of this, chemists pointed out in their packaging inserts that when administered by injection the vaccine could work 'very differently on different people', so they were unable to provide 'any general instructions for use'. They also warned that, 'inappropriately used, the house-dust vaccine is a very dangerous

substance' and that it was not to be used 'without knowledge of the literature on the subject'.[22]

Allergological Laboratory

Nevertheless, demand grew and, in January 1944, Barfod was able to employ a full-time manager to take care of the production and sale of preparations. He recruited law student Helle Olrik (who also happened to be his daughter-in-law's sister). Gradually, production increased until it had grown to the extent that it had to be separated from the general pharmacy operations. In 1949, Barfod set up the Allergological Laboratory, with Olrik as 'laboratory superintendent'. Despite the new enterprise, production continued in Frihavn Pharmacy as well.[23]

Production was not the only element of the work, however, and Barfod was still co-operating with doctors investigating causes and treatments of allergies. In 1946, working with allergologist E. Winge Flensborg, he published an article in *Ugeskrift for Læger* on 'The Significance of Mould Fungi as Allergens in Asthma in Children'.[24]

The significance of his work was duly recognised on 7 July 1949, when Barfod received another royal honour, the Order of the Dannebrog, for his 'immense contribution to the production of preparations for the examination of patients suffering from allergies' and for his 'important research'.[25]

Barfod's collaboration with Baagøe also took on a new dimension when the two men helped found the Dansk Selskab for Allergiforskning (Danish Association for Allergy Research) and the Nordisk Selskab for Allergologi (Nordic Allergology Association) in 1946. Baagøe sat on the governing bodies of both associations and, in September 1947, was President of the first Nordic allergy congress, held in Copenhagen.

By and large, allergology was gaining ground, with an increasing amount of research being conducted in the field. An asthma-allergy clinic for adults was set up at the Rigshospital in 1941, followed by a corresponding clinic for children in 1956. These developments meant

Helle Olrik, Superintendent, later Managing Director 1944-1977.

there was a growing demand for allergen preparations. In June 1956, the Allergological Laboratory was granted the status of controlled laboratory, which meant that it was licensed by the Ministry of Justice – under the auspices of the National Board of Health – to sell its preparations to other pharmacies. The licence specified that the laboratory was 'solely required to supply allergens for diagnostic, therapeutic and prophylactic treatment'.[26]

The regulatory framework for production and laboratory organisation was becoming increasingly strict, and demand was growing too.

Consequently, the Allergological Laboratory moved out of Frihavn Pharmacy the following year, to take up residence in its own fifth-floor premises at Kronprinsessegade 54. In the same year, Barfod celebrated his 80th birthday and, as he prepared for retirement, the question of the laboratory's future arose.

On 9 August 1961, the Allergological Laboratory was transformed into a limited company founded by Barfod together with his son, Assistant Professor Hans Peter Barfod, and Helle Olrik. The purpose of the company was the 'production and sales of preparations for the treatment of allergic illnesses and other medicinal preparations'. Share capital was DKK 50,000, of which Peter Barfod subscribed DKK 24,000 on 1 August by transferring the laboratory with all its assets and liabilities to the new company, while Helle Olrik and Hans Peter Barfod subscribed DKK 24,000 and DKK 2,000 respectively, in cash. The three shareholders formed the board of the company, with Olrik holding the post of Managing Director with full executive authority.[27]

A new era in the history of the Allergological Laboratory had commenced.

Allergological Laboratory exhibits its products at the Panum Institute, Copenhagen 1953.

2.

Scientific breakthrough

The Allergological Laboratory's turnover rose steadily by an average of 10% p.a. throughout the 1960s, passing the DKK 1 million mark in 1967 and reaching DKK 1.5 million in 1970. The main customers were Danish pharmacies, the Rigshospital's two allergy clinics and Danish specialists who ordered allergens mixed specifically for their patients. Such detailed prescriptions (ordered by phone) might specify, for example, 30% cat hair, 50% house dust and 20% pollen – a combination probably based on experience.

An export market soon opened up in Scandinavia, particularly in Norway, where a number of leading allergologists used the Laboratory's preparations. In 1969, exports accounted for 40% of turnover.

Meanwhile, the National Board of Health was imposing increasingly strict requirements on production so, in January 1968, the Allergological Laboratory employed its first trained pharmacist, Dorde Venov. There were now eight full-time members of staff, as well as a part-time errand girl. In September 1968, another graduate arrived in the shape of Suzanne Gravesen, a biologist and fungal expert. Gravesen was responsible for improving the systematic production of mould, and analysing mould in the homes of allergic children. This pioneering work, which went beyond diagnosis to analysis of the patient's environment, was carried out in collaboration with Knud Wilken-Jensen, a consultant at the Child Allergy Clinic at the Rigshospital.

By the mid-1960s, the premises at Kronprinsessegade were becoming crowded, a problem that was remedied in 1967 when the addition of an adjoining property doubled their size. After major renovations, there was enough room for expansion and all fifteen employees who were working there by 1970.

Specific immunotherapy

Although the facilities and apparatus at the Allergological Laboratory were modern by comparison with Frihavn Pharmacy, the extracts were still produced manually, using methods that were typical in laboratories and pharmacies. The business of acquiring raw materials was a story in itself. Cow hair came from the state experimental farm in Hillerød, while the Royal Veterinary and Agricultural College supplied cat hair. The Laboratory advertised for human hair in a hairdressing publication (providing guidelines for keeping male and female hair separate). It was particularly difficult to obtain sufficient quantities of house dust so everyone, from staff to customers, was asked to donate the contents of their vacuum cleaners to the Laboratory. The one raw material that was produced by the Laboratory itself was mould, which was grown in a special unit.

By and large, production still followed the guidelines used in Frihavn Pharmacy in the 1930s. The scratching and pricking of dried extracts into the skin had been replaced with other procedures, however, such as dripping allergen solutions into the eye, sniffing allergen powders or inhaling steam from allergen solutions. Dried extracts were dissolved in aseptic dilutants of sterile water in varying strengths, which were injected into patients in concentrations rising from 1:10,000,000 to 1:100. Consultant Egon Bruun of the Adult Allergy Clinic at the Rigshospital controlled the biological content of the preparations.

One measure of the increased understanding of the causes of allergies and the mechanisms of treatment effects, was the emergence of the term 'desensitisation' to replace 'vaccination'. In the 1920s and 1930s, it was postulated that treatment led patients to develop antibodies against the allergy-inducing substance. Now, it was known that treatment affected the immune system's reaction pattern to the allergy-inducing substance and improved the patient's ability to tolerate the substance. A further expression of this new recognition was the gradual introduction of the term 'specific immunotherapy', indicating that treatment is specific to the allergy-inducing substance in question.

As had been the case in the 1930s, treatment still had a seasonal aspect, with patients receiving preventative injections in the months leading up to the grass pollen season, for example. Then again, the ongoing effects of an allergy-inducing substance could also be counteracted if, following the administration of gradually increasing doses, the patient regularly received the strongest injection as a 'maintenance dose'.[28]

The Allpyral challenge

Over the years, the Allergological Laboratory had built up a stable, regular clientele. Many patients returned year after year for preventive treatment ahead of the pollen season, and there was a steady influx of new patients. On the whole, the Laboratory found itself almost alone in a specialised market. Competitors were few and far between and lacked any foothold in Denmark. However, in spring 1967, Helle Olrik returned from an allergy conference in Brussels to report that there was a new, patented method of producing preparations and that the company who owned the patent had applied for authorisation in Denmark.[29]

The method had been developed in the USA, where Miles Dome Laboratories had launched a new grass pollen preparation on the international market in 1963, under the name Allpyral Grass Mix. Unlike the Allergological Laboratory's preparations, it was not water-based but bound to aluminium and dissolved in pyridrine.[30]

Egon Bruun tested the new preparation on 88 patients at the Rigshospital and the results were published in *Ugeskrift for Læger* in 1967. They were unambiguously positive; not only did treatment with Allpyral give results that were as good as water-based preparations, but it also achieved the same effect with only a third of the number of injections. In addition, there was a reduced risk of allergic reactions to the injections with Allpyral, and tests had not revealed a single case of allergic shock reaction – presumably because the body absorbed the active substances more slowly than water-based solutions.[31]

The advantages for patients were clear. Treatment with water-based preparations typically took around three months, and injections had to be given every two or three days. Now, the number of injections could be greatly reduced, with longer intervals between them, with a reduced risk of allergic reactions, particularly allergic shock reactions, as well. Allpyral was not yet approved for use in Denmark, but it would only be a matter of time before it posed an obvious threat to the Allergological Laboratory's market position. Despite all its advantages, Allpyral had not overcome a fundamental problem: nobody knew precisely what the contents of the preparations were and nobody knew how they worked, so it was still not possible to manufacture standardised products.

Allergological Laboratory, Kronprinsessegade, Copenhagen 1972.

Nevertheless, the emergence of Allpyral was a warning of what the near future would bring. It was the first real innovation in allergy treatment for almost half a century – but not the last. In fact, research into allergies, their causes, their diagnosis and possible treatments for them, was approaching a major turning point, not least in Denmark, where the Allergological Laboratory would be pivotal in a decisive breakthrough.

The global launch of Allpyral also demonstrated that the market was undergoing a fundamental change and becoming globalised, and that this would pose challenges for the future business of the Allergological Laboratory as well.

Coffee break at the Protein Laboratory. From left to right Gitte Nordskov Hansen, Kirsten Billesbølle, Peter Lind, Kai Danielsen, Henning Løwenstein.

Protein Laboratory and Allergy Club

In 1967, two groups of researchers into antibodies, working independently of each other in the USA and Sweden, discovered the human antibody immuno-globulin E (IgE), which induces overreactions in response to external substances, thus causing allergic reactions and asthma. This 'allergy antibody', as it was called, was chemically specific, and its discovery was nothing short of revolutionary. It led pharmaceutical companies, laboratories and researchers all over the world to take a serious interest in allergens.

Staff meeting at 'Ved Amagerbanen 23', 1979. Amongst others Ellen Nielsen (above, to the right) and Astrid Thomsen (below, in the middle).

In Sweden, researchers succeeded in developing a method known as the radioallergosorbent test (RAST), which used blood tests to analyse whether a patient was allergic to dogs, cats, grass, birch pollen, or something else, making it possible for the first time to measure the strength of allergen extracts used in treatment. The Swedish medicinal company Pharmacia patented the method. A breakthrough was also made in Denmark, despite a shortage of financial (though not human) resources.

A young doctor, Bent Weeke (born 1936) and the even younger chemist Henning Løwenstein (born 1939) both began work at the University of Copenhagen Protein Laboratory in 1967. Løwenstein resigned following a disagreement with Niels Harboe, founder and director of the Protein Laboratory, but Harboe lured him back with a tailor-made deal in 1970. The arrangement was that Løwenstein would be employed by a private company, Chr. Hansens Laboratorium A/S, but would spend half of his working time in the Protein Laboratory, researching immunoglobulins and other serum proteins.

Weeke, who was working on a doctoral thesis on the identification of human serum proteins with the help of immunoelectrophoresis, wondered what allergen extracts might contain. Since the Allergological Laboratory was unable to furnish him with an answer, he suggested in early 1972 that Løwenstein should conduct an amino acid analysis on house dust extract. His suggestion was not positively received, and Løwenstein ended up conducting an analysis of pollen extract instead. Løwenstein did not know much about allergy at the time but his scientific work was, nevertheless, instrumental in a breakthrough that facilitated the standardisation of allergen extracts.

His work formed the foundation for the development of a technique for analysing both pollen and house dust. At this point, progress really took off. Within a short period of time, Løwenstein and Weeke were able to identify cat hair, mites, mould and pollen in dust, as well as many of the proteins in pollen. Their results, which were presented to the European Allergy Congress in Oslo in August 1972, provided new opportunities to find out what actually provoked allergies.

Right from the very beginning, Dorde Venov and Suzanne Gravesen at the Allergological Laboratory followed the collaboration between Løwenstein and Weeke with great interest. Before long, the four of them were getting together at the Laboratory in Kronprinsessegade with other researchers, doctors and laboratory staff for informal meetings to discuss the mysteries of allergies. In the spirit of Baagøe and Barfod, the 'Allergy Club' (as the exclusive circle was known) exchanged information and ideas across institutions, disciplines and professions, in an atmosphere of informality, creativity and mutual inspiration. 'A small club has been set up with ten or so new scientists as members,' Helle Olrik wrote to Kaj Baagøe: 'They are saying straight out that they don't want "the old ones" taking part, otherwise it will become far too stiff and formalised.'[32]

Everyone was fired up by the expectation that Weeke and Løwenstein's discoveries would lead to a genuine breakthrough in the treatment of allergy – and the outlook was certainly promising.

Within six months of their presentation to the allergy congress in Oslo, Løwenstein and Weeke had developed a technique that made it possible to identify, very precisely, the proteins that induced allergy in the individual patient. They also demonstrated that every patient has an individual reaction pattern but that there are particular allergens in each allergy-inducing substance to which most patients react strongly (major allergens) and other allergens to which patients typically react less strongly (minor allergens). They presented these discoveries at the European Allergy Congress in Helsinki in the early summer of 1973, where they attracted well-deserved attention. Researchers around the globe knew the new method of analysis as 'crossed radioimmunoelectrophoresis', and it set off a process that was to have a decisive influence on the future development of the Allergological Laboratory.

The first European Allergy Congress (EAACI) in Paris, 1950.

‘… A small club has been set up with ten or so new scientists as members. They are saying straight out that they don’t want “the old ones” taking part, otherwise it will become far too stiff and formalised.’

Managing Director Helle Olrik to allergy pioneer Kaj Baagøe

Move to Amager

Ever since Baagøe and Barfod started the production of extracts for treating allergies back in the 1920s, the inability to standardise preparations had been the main problem faced by allergology. At a Nordic level, work had been going on since 1946 to develop a method of standardisation, but it was only now, using the Løwenstein/Weeke method, that standardisation became possible on the basis of defined, objective criteria. The aim was to control the content and strength of extracts according to the requirements of each individual allergy patient and produce preparations in precise, prescribed concentrations.

Løwenstein gradually started to focus solely on allergy work. He returned to the Protein Laboratory on a full-time basis in 1972, and in 1974 he proposed to Olrik that he should become consultant to the Allergological Laboratory, with a view to developing a standardisation programme and setting up a completely new specialised laboratory. A deal was struck and Løwenstein began working one day a week at the Allergological Laboratory. With him as the driving force, work commenced on plans to produce the first standardised allergen preparations.

It was at this time that Allpyral was approved for use in Denmark. As well as its advantages in terms of treatment, its doses were stated in protein units and not (as was the case for the Allergological Laboratory’s preparations) by weight/volume, so it quickly gained preferential status at the Rigshospital. Doctors diagnosed patients using Danish extracts, but then prescribed American preparations for treatment. Other non-Danish competitors used similar methods but the immediate threat was from Allpyral, and the Allergological Laboratory found itself in an unsustainable situation that threatened its very existence. The Laboratory survived the immediate threat after it managed to obtain a French formula for binding allergens to aluminium hydroxide based on Alhydrogel, an aluminium hydroxide gel manufactured by the Danish company Superfos. Soon, it was busy producing extracts based on the French formula.

The storm seemed to have subsided, but it was clear that the Allergological Laboratory was at a crossroads. International competitors were beginning to exert serious pressure and, even though the discoveries of Weeke and Løwenstein had tremendous market potential in Denmark and abroad, major investment was needed in research and development as well as production.

There was also a pressing need to find premises that were larger and better equipped than those at Kronprinsessegade, especially since the National Board of Health had introduced stricter requirements for sterile environments. A property at Ved Amagerbanen 23 was purchased on 1 June 1974, in which the Laboratory's staff – now expanded to twenty – would enjoy almost three times more space. The purchase price was DKK 2.3 million, but on top of this came the cost of new laboratory facilities, including an isotope laboratory where work could begin on the standardisation of extracts on 'a genuine allergen determination using the method of Dr Weeke and Master Løwenstein,' as Olrik put it.[33]

Scientific breakthrough and standardisation

The move took place in 1975, and Løwenstein's first task was to supervise the equipping of the new laboratory. Under his direction, the standardisation project was now able to begin. The Allergological Laboratory was not alone, with Norway's Nyco and Sweden's Pharmacia also seeking standardisation. The Danes, however, were the first to succeed.

In 1976, under the title Dansk Samarbejde om Allergen Standardisering (Danish Co-operation on Allergen Standardisation), Løwenstein and Weeke launched a scientific research project in which hospitals and clinics around the country which treated allergy patients were asked to participate. This was rather an unusual collaborative venture for its time, between private enterprise and a university laboratory.

Using raw materials from the Allergological Laboratory, the Protein Laboratory prepared a range of different extracts. These were sent to

In 1975, Allergological Laboratory moves to new premises at 'Ved Amagerbanen 23'.

Danish doctors and specialists to test on their patients. Blood samples taken using the Swedish RAST method were then sent to Weeke at the Rigshospital. With the help of the biotechnology company Dakopatts, founded by Niels Harboe in 1961 – yet another private enterprise with its origins in the Protein Laboratory – antibodies were produced for use by Løwenstein in crossed immunoelectrophoresis.[34]

This project, known as DAS 76, resulted in the first procedure in the world successfully to characterise and standardise allergen

extracts. Its participation in this scientific breakthrough was crucial to the Allergological Laboratory, in that it gained access to the new method of developing preparations for allergy treatment. This was the definitive breakthrough for the manufacture of standardised products. However, to control the preparations, it was necessary to analyse patient serum samples and determine which substances were inducing allergic reactions, and this meant that funds were needed for a new diagnosis laboratory – funds that neither the Laboratory nor its owners possessed.

Crisis – and rescue

The purchase of the new premises at Ved Amagerbanen 23 and the investment in new facilities had placed a heavy burden on finances and, in 1975, for the first time in its history, the Allergological Laboratory posted a deficit. By the summer of 1976 it was clear that, despite higher turnover, the company was again heading for a loss. Venov, Gravesen and a newly appointed pharmacist, Bente Schwartz, approached Olrik and the board with a request for increased investment in development and laboratory facilities – a request backed by Løwenstein.[35]

The Laboratory was under pressure from other sources too. Allpyral had siezed a large share of the market and was gradually becoming the dominant grass pollen vaccine. The Allergological Laboratory was no longer the biggest player in the Danish allergy vaccine market and, although it was ready to market its own hydrogel-based product, its condition was critical. In the Rigshospital, Weeke was threatening to set up his own laboratory and was also negotiating with Miles Dome Laboratories in the USA. Løwenstein was also calling for 'action, instead of a wait-and-see attitude'. Finally, Olrik and the other owners gave in to the pressure.[36]

In September 1976, Olrik opened negotiations with the Lundbeck Foundation about the sale of the Allergological Laboratory. The connection had been made through banker Erik Birger Christensen, who sat on the board of the Lundbeck Foundation. He was also the father of Suzanne Gravesen, who had paved the way for a deal. The starting point was a valuation of the shares (nominal value DKK 1,000) at DKK 1,140 each, but Olrik was also negotiating with another prospective buyer.

On 26 January 1977, Novo Industri A/S entered into an agreement with Olrik and the other owners of Allergological Laboratory to buy the whole share capital at a price per share of DKK 2,500, or a total of DKK 2.5 million. In addition, Olrik would be employed as consultant for a five-year period at an annual index-linked fee of DKK 250,000 plus pension. Later that day, the deal was presented to the Laboratory's staff by Olrik, together with Mads Øvlisen and Jan Leschly from Novo – and the reaction was swift.[37]

Led by Venov and Gravesen, ten key members of staff announced that they would resign if the takeover went ahead. Løwenstein was offered a top post in Novo Nordisk by Øvlisen, Leschly and Lars Josefsson, the Novo Group Director of Research, but he remained in solidarity with the rest of the staff. That evening, both parties had to accept that the basis for any agreement had vanished; without Løwenstein and its key members of staff, the Allergological Laboratory was worth nothing, so the deal was called off. Formally, the purchase offer remained on the table until 15 February, while the Lundbeck Foundation was offered the Laboratory on the same terms.[38]

The staff reaction stemmed from concern that Novo was only interested in the Laboratory's facilities and Løwenstein's knowledge of protein chemistry, so there was much celebration when the Lundbeck Foundation accepted a deal on the same terms and conditions that had been negotiated with Novo Industri.[39]

The deal was approved by an extraordinary general meeting of the Allergological Laboratory on Friday 25 February 1977. A new board took over and Olrik announced her resignation as Executive Director with effect from 1 February. The new board consisted of: Børge Sørensen (Chairman), a director of the Lundbeck Foundation; Holger Byfeldt, a director of Lundbeck & Co A/S; and Niels Harboe. Holger Byfeldt was appointed Acting Executive Director of the Laboratory.[40]

World's first standardised allergen preparation

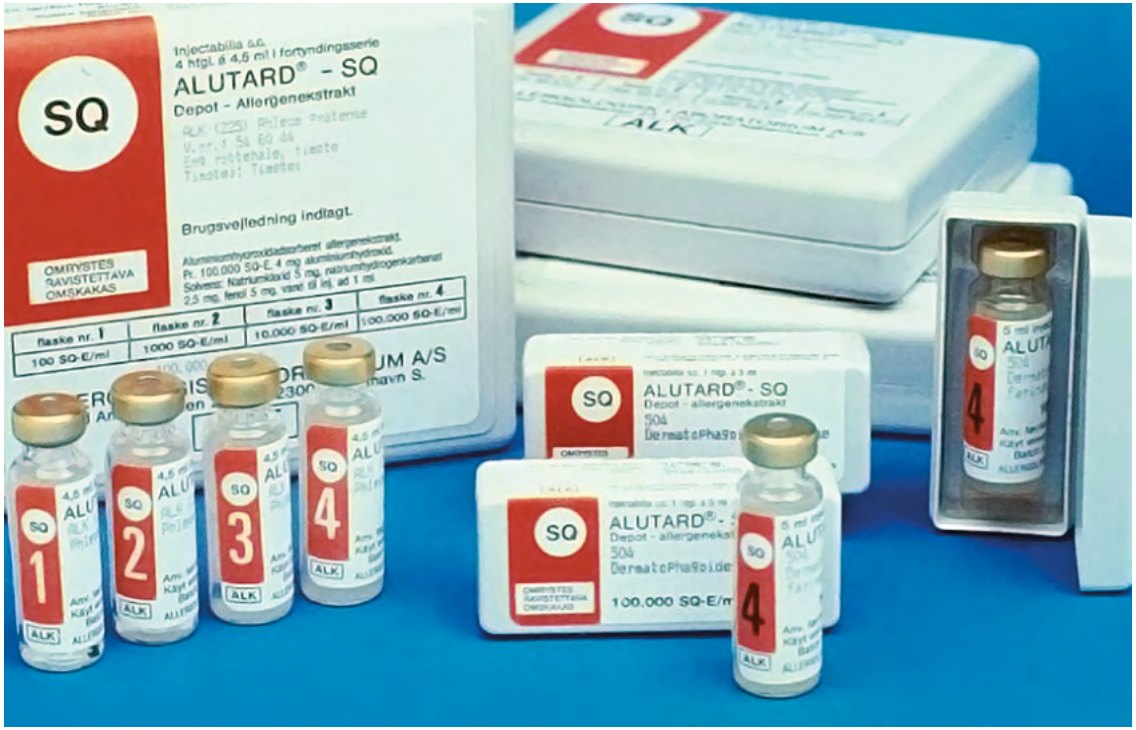
The satisfaction of the staff seemed, at the time, to be justified. In the midst of all this turbulence, in January 1976, the Laboratory had sent the first aluminium hydroxide-based extracts for clinical trials. Before long, it was able to market a mite extract and a grass pollen extract and compete with Allpyral.

In June, DKK 900,000 of new capital was injected into the Laboratory when the Lundbeck Foundation raised the share capital to DKK 1 million, a move that eased the immediate financial pressure. Perhaps more importantly, further investment materialised when, in August, the Lundbeck Foundation established a new company, Diagnoselaboratoriet af 1977 A/S (Diagnostic Laboratory), with share capital of DKK 250,000. The board of the new company was identical to that of the Allergological Laboratory. The Managing Director of both was Bjarne Knudsen, who had been head-hunted from the company that marketed Allpyral in Denmark. The idea was for the two laboratories to work closely together.[41]

The Diagnostic Laboratory had been set up to analyse serum samples to determine which substances patients were allergic to. It functioned as a service laboratory for allergy doctors in Danish hospitals, who sent in patient serum samples for testing. But it also offered antigen analysis of patients' environments to determine the presence of such items as micro-fungi, animal hair and dust mites. In a somewhat less precise manner, the Diagnostic Laboratory also offered to analyse house dust suspected of causing allergy by looking for 'something' in the patient's environment. The analysis started with the contents of the vacuum cleaner, as per the 'old days', but using far more advanced techniques.[42]

A big step forward came in 1978, however, when the Allergological Laboratory became the first in the world to market standardised allergen extracts, known as SQ (Standardised Quality) extracts. It was decided to market the product line internationally under the trademark ALUTARD SQ. Considerable investment was required, not only in research and development in order to maintain its head start on competitors, but also in production facilities and setting up an international sales and marketing organisation.

Alutard SQ launched in 1978.



Under the wing of Chr. Hansen

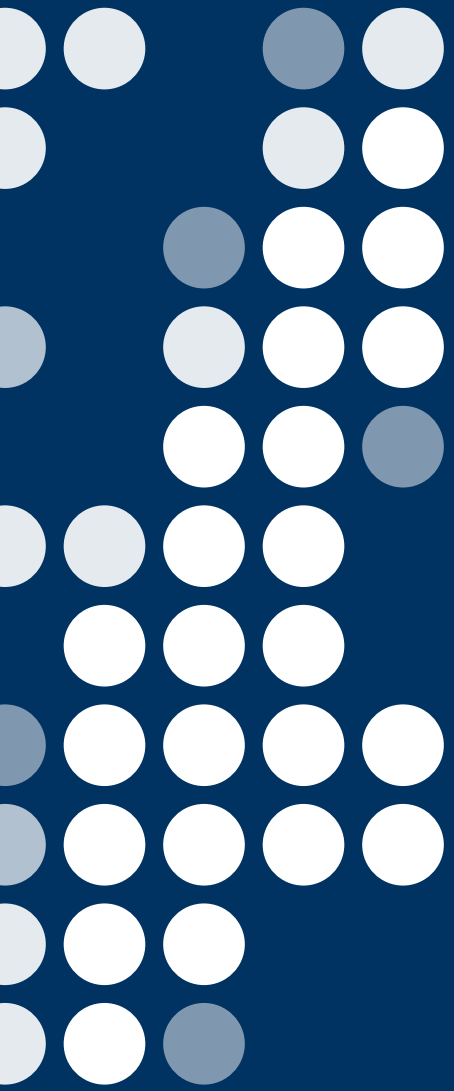
The potential for the Laboratory's methods and products was huge, but its finances were still strained, with no prospect of improvement. Quite the reverse, in fact – the 1977 accounts showed a loss of DKK 997,350 on turnover of DKK 3,834,000. The situation deteriorated in 1978, with a loss of DKK 1,258,821 on turnover that had slipped to DKK 3,751,000. Further capital and resources were needed, but the Lundbeck Foundation declined. A capital injection of DKK 1 million was provided by the expansion of the share capital at the end of 1978, but it was far from sufficient.[43] By the summer of 1979 it was clear that the Laboratory was heading for more red ink on the bottom line and its equity was close to zero.

It was not just the staff who were frustrated by the lack of commitment from the Lundbeck Foundation. Harboe wanted to see some action, too, but felt unable to change the minds of the Foundation's directors, even though he had joined the board of the Foundation in 1978. Instead, he began working with Chr. Hansens Laboratorium A/S, where he was a board member and a nominee director in the company's executive management at its headquarters in Sankt Annæ Plads.

Chr. Hansen already had enough on its plate. The company was in big trouble and its bottom line, too, was in the red. Following the death of its Managing Director Svend Munk Plum in May 1976, Harboe had become the board's nominee director in a provisional management team. In November 1976, Steen Engel took over as Managing Director. Although there was more than enough work to be done getting Chr. Hansen back on an even keel, Harboe succeeded in convincing not only Engel but also other key members of the management team that it would be a good idea to take over the Allergological Laboratory. It probably helped that Harboe's wife, Annelise Uldall-Hansen, was Christian Hansen's grand-daughter and a major shareholder in the company.

In autumn 1979, Chr. Hansens Laboratorium bought out all of the equity in both the Allergological Laboratory and the Diagnostic Laboratory from the Lundbeck Foundation. The accounts presented a counter-argument, but the combination of Harboe's powers of persuasion and a thorough, business-like analysis of the Laboratory's finances and prospects won the day. Engel became the new Chairman of the Board, Barfod kept his seat and Torben Riese of Chr. Hansen joined the board.[44] That left the matter of appointing a Managing Director who could and would take on the job of expanding the financially unsteady Allergological Laboratory into the international market.

The choice was 32-year-old Elsebeth Budolfsen, a pharmacology graduate who had been a director in Novo Nordisk A/S since 1977. Having worked for Swedish Pharmacia in 1972-73 and Netherlands-based Organon Int. B.V. Ercopharm in 1973-77, Elsebeth Budolfsen had experience of international markets. The Allergological Laboratory's position was far from optimal, but Budolfsen was persuaded, partly by the products but also by the commitment of the thirty members of staff and pledges of support and financial backing from Chr. Hansen.



3.

From laboratory to global concern

Elsebeth Budolfsen, CEO 1979-2000.

Budolfsen was appointed Managing Director of both the Allergological Laboratory and the Diagnostic Laboratory on 3 December 1979. The financial situation for the two laboratories was presented at a board meeting two weeks later, and it did not look good. The Allergological Laboratory was in particularly dire straits, with cash reserves of just DKK 48,000 - and even that was only due to an overdraft facility of DKK 700,000 being utilised to its full extent. Since the takeover, Chr. Hansen had provided loans totalling DKK 475,000 to keep the Laboratory running, in addition to which the Lundbeck Foundation had provided credit of about DKK 3 million, and the Laboratory wanted to pay this off by increasing its overdraft facility.[45]

The Laboratory was not in the best of financial health, in other words; and when the results for 1979 were calculated, the accounts showed a deficit of DKK 1,152,000, while the balance sheet was burdened by significant debt – and a negative net equity of DKK 100,000.[46] The bad results came as no surprise. Before the takeover, Chr. Hansen had investigated the Laboratory's finances thoroughly and had drawn up an action plan for recovery that would turn it into a profitable company again within four to five years.

The idea was not for the Allergological Laboratory to be integrated into Chr. Hansen, but for it to be allowed to develop research, products and marketing in its own right. Both Harboe and Engel were guarantors for this. The Laboratory was to stand on its own feet and, as owner and investor, Chr. Hansen was willing to take the risk, trusting that the trend could be reversed. On paper, this may have seemed an achievable task; in practice, a difficult and laborious job awaited them.

'Saved by Austria'

It was clear from the outset that the Danish market, and even the entire Scandinavian market, was of insufficient size to generate enough turnover to finance the research and development that would be needed if the Allergological Laboratory's SQ products were to be anything other than a flash in the pan on the international market for allergen extracts. Building an international sales and marketing organisation was, therefore, part of the strategy right from the start. This called not only for greater resources but also for deeper insights into the Laboratory's products, competing products and the specialist market at which the products were aimed.

The international breakthrough proved difficult to achieve. The Danish company was almost unknown outside its traditional markets in Scandinavia (where it was best known in Norway). But not only that – the Allergological Laboratory was also far less well-known than its competitors and didn't have the same level of funding available for marketing, so even though it was far ahead of the competition in terms of knowledge and expertise, it lagged behind as far as international position and resources were concerned.

On the face of it, it looked as if the downward trend would continue. The first year under Chr. Hansen's ownership ended with the Allergological Laboratory posting a loss of DKK 1.9 million. The following year

was even worse, with a deficit of over DKK 3 million. At the end of 1981-82, the bottom line was still in the red, this time to the tune of DKK 1.8 million, while negative net equity had grown to almost DKK 7 million.[47]

There was growing concern about whether a turning point would ever be reached, but Chr. Hansen maintained its faith in the Allergological Laboratory and continued to fund its operations. And there did seem to be some light at the end of the tunnel. At its annual general meeting on 14 February 1983, the board was able to announce that the turnover in the past financial year had grown by more than DKK 1.5 million (or 28%) to almost DKK 7.8 million and that, even though there was still a deficit, this had been reduced by DKK 1.3 million. The conclusion was that all their endeavours had 'started to bear fruit'. Contributing to this evaluation was undoubtedly the fact that the company had indeed reached a turning point.[48]

The catalyst had been a trip to Vienna in 1981, when Budolfsen succeeded in arousing the interest of the Austrian company Epipharm, the national distributor of allergen preparations from the Spanish company Abelló. The following year, when the Allergological Laboratory flew its colours abroad for the first time, with a small exhibition at an international allergy congress in London, a representative of Epipharm sought out the Danes and asked whether the Allergological Laboratory would be interested in taking over Abelló's position in the Austrian market. Indeed it was.

For the Austrians, this was a major operation. The Spanish preparations had to be replaced with Danish ones; all the supplies to doctors, specialists and from there to the patients had to be adapted; and everyone involved had to be convinced that the SQ products were an improvement. But it was a success. In one fell swoop, the Allergological Laboratory had conquered a new market, and in December 1983, when Budolfsen presented the annual accounts, turnover in 1982-83 had increased by a whole 52% to DKK 11.5 million and the bottom line was black for the first time since 1974, with a profit of DKK 642,000.[49]

This was not the only benefit to emerge from participation in the London conference. Relationships were forged with a number of other international contacts including distributors such as the British company Fisons and Scherax in Germany, a subsidiary of the large German pharmaceutical group Schering. The breakthrough into the Austrian market was the crucial advance, though, coming as it did at a time when it was vital for Chr. Hansen's investment and endeavours to start to bear fruit. 'Saved by Austria' was how the Allergological Laboratory's staff later dubbed the breakthrough.

Journey to America

In 1982, Budolfsen visited the USA to forge the first of the contacts that would open up the enormous American market. Her destination was Baltimore, home of one of the USA's largest research and training hospitals in the field of allergies. She hoped to interest the doctors there in Danish preparations. The Allergological Laboratory was one of the first Danish pharmaceutical companies to move into the American market, however, and was completely unknown. The way forward was helped by Løwenstein's international reputation.

ALK-Abelló, Inc., Round Rock, Texas, USA.

It also helped that the Allergological Laboratory was able to refer to Kaj Baagøe and point to the fact that, historically, the Danish company and its products could be traced to an American source. In a sense, it was going back to its roots, this time bringing the Allergological Laboratory's SQ preparations back across the Atlantic – preparations that were better than the American ones.

The purpose of Budolfsen's trip to the USA was twofold: to find a company to represent the Allergological Laboratory and distribute its products; and to overcome the barrier represented by the Food and Drug Administration (FDA), part of the American Department of Health and Social Services. The FDA's registration and strict approval procedures were – and remain – a requirement for anyone wishing to market medicines, foodstuffs and other products in the USA.

Budolfsen had to drop the idea of finding a suitable American partner, but did succeed in persuading the FDA to conduct a pre-inspection of the Allergological Laboratory's research and production facilities in Denmark. At that time, this was something not many other Danish companies had managed. An American inspector duly crossed the Atlantic to scrutinise the premises at Ved Amagerbanen 23. His findings were beyond all expectations. The FDA requested a number of changes, but in principle it was positive, and the Allergological Laboratory was able to apply for product registration of the first preparations.

In spring 1984, the Allergological Laboratory set up its own sales company, ALK America Inc., in Newhaven, Connecticut. Two of the new company's three employees had been directors at Miles Dome Laboratories, which had developed Allpyral. The FDA had not yet approved any of the Laboratory's products, but the Laboratory went ahead with the investment, confident that it soon would.

The FDA's first approval of a preparation was granted later that year but, paradoxically, the Danish methods and preparations were too advanced for the USA and the FDA had neither the equipment nor the competence to test the SQ standard. As a result, the Allergological Laboratory had to manufacture a special preparation, of poorer quality, for the American market. This was awkward and frustrating, but at least it meant that the marketing and introductory sales could commence. The FDA granted final approval for the production facilities at Ved Amagerbanen 23 in 1985. Although, to the disappointment of management and staff, the FDA took longer to grant approval of other preparations, the Allergological Laboratory's first bridgehead had been established in the American market.[50]

In 1986 Allergological Laboratory formally changed its name to ALK as an abbreviation of Allergologisk Laboratorium København (Allergological Laboratory Copenhagen).

Acquisition of Pharmacia's product line

By the mid-1980s, the Allergological Laboratory had become a serious player in the international allergy products market. At the same time, it was starting to feel the effects of competition from other companies, in particular from the Swedish company Pharmacia, a very large multinational pharmaceutical company with a wide range of products.

Pharmacia had developed a number of high-quality allergy vaccines, using its own RAST method of diagnosis and a copy of the Danish methods of standardisation, which had not been patented. The Swedish company had poured considerable resources into marketing and, although this had not secured the desired degree of progress, it was enough for the Allergological Laboratory to feel the effects of competing with its 'Pharmalgen' line.

Evidently, Pharmacia was also feeling the pressure from its Danish competitor. At any rate, early in 1986 the Swedish company made Chr. Hansen an offer of collaboration, suggesting this might take the form of the establishment of a joint allergy company or, alternatively, a Swedish acquisition of the Allergological Laboratory.

Neither of the offers was positively received in Denmark. Under no circumstances was the Allergological Laboratory for sale, and collaboration lacked appeal because of the difference in the size of the two companies. As an alternative, Engel and Budolfsen proposed that the Allergological Laboratory should take over all Pharmacia's allergy vaccine products. It would seem that Pharmacia had envisaged a sell-off as a possible outcome of the negotiations, and it did not take the Swedes long to accept.

In November 1986, the Allergological Laboratory took over the whole Pharmalgen line from Pharmacia. The move immediately boosted turnover and significantly improved the Laboratory's position in Europe, where it entered a number of new markets, and also, more crucially, in Canada and the USA, where the Allergological Laboratory was still struggling to have its preparations approved.[51]

The fact that the takeover had expanded the Laboratory's product range was also crucial - Pharmalgen was a global market leader

in vaccines against allergy to bee stings and other insect venoms, which had not previously been part of the Laboratory's portfolio. In connection with the takeover, it was agreed that the Danes would spend eighteen months learning the Swedish production processes, including an advanced freeze-drying technique, so that production could be transferred to Denmark.

Included in the acquisition was Pharmacia's Dutch company, Laboratorium Diephuis BV, as well as a small American company, Vespa Laboratories Inc. Despite its modest size, Vespa Laboratories was highly significant as it was the only producer of bee and wasp venom in the world, and these were raw materials in the production of vaccines against insect sting allergy. In other words, the Allergological Laboratory had guaranteed the control of the supply of raw materials not only to itself but also to its competitors.[52]

'Save immunotherapy'

The fact that Pharmacia eventually agreed to sell, rather than buy, might have had to do with the fact that the market had stagnated for allergy vaccines – or specific immunotherapy, as it had become known. In several countries, it had almost completely ground to a halt. The stagnation was caused by a number of cases (e.g., in Britain) where patients had died as a result of allergic shock brought on by too high a dose of active substances. The result was a widespread scepticism towards the treatment method, not only in Britain but also in the rest of Europe, including Denmark, where the use of allergen preparations decreased and the number of patients referred to the allergy clinic at the Rigshospital fell sharply.

The Allergological Laboratory was hit by this general discrediting of immunotherapy, too, even though none of its products had caused any of the deaths. Immunotherapy suffered hard times in the late 1980s. To boost the Allergological Laboratory's market position and to 'save immunotherapy', a massive marketing campaign was drawn up. It was directed at allergy doctors and specialists in specific countries, primarily in Austria and the large, absolutely crucial German market.

The campaign focused on explaining to allergy doctors and specialists that, because of the SQ technology it used, the Allergological Laboratory's products were better than the competition's. Doctors and specialists were invited to Denmark to attend lectures on allergy, allergen preparations, treatment methods – and the SQ technology.

It was a wide-ranging campaign, especially in the major German market. Wednesday after Wednesday after Wednesday, meetings were held with doctors flown in from Germany. On returning to their practices, the doctors and the specialists were then contacted by the Allergological Laboratory's distributor, Scherax, which represented the SQ products. Results quickly manifested in the form of high growth rates on the German market.

The campaign improved the market position of the Allergological Laboratory and helped restore faith in immunotherapy.

The move to Hørsholm

The acquisition of the Pharmalgen line was the Allergological Laboratory's passport to the international market for allergy products, and it now had distribution and production companies in a number of countries. This placed new demands on the organisation of the company. In a relatively short time, it had been transformed from a laboratory almost entirely active in its domestic market to a globally oriented company.

Immediately after the acquisition, the Allergological Laboratory took over ALK-America, which had previously been owned by Chr. Hansen. The company assumed responsibility for the distribution of Pharmalgen (side by side with the Allergological Laboratory's own products) in the USA and Canada and started to build up a sales and marketing department. With the addition of its first wholly owned subsidiary, the Allergological Laboratory formally changed its name to ALK as an abbreviation of Allergologisk Laboratorium København (Allergological Laboratory Copenhagen). The name change was occasioned by marketing needs abroad, especially in the USA, where ALK had been used in the American subsidiary's official name right from the start.

The first time ALK was used in an annual report was in 1986-87, but in fact the abbreviation had been in unofficial use as in-house jargon since the 1960s, with the 'K' standing for Kronprinsessegade. Gradually, the acronym had caught on externally as well, especially among users of ALK's products in the Norwegian market, for whom the abbreviation was a way to distinguish the Danish laboratory from a similar local producer of allergy vaccines. Now, the abbreviation was used to meet the new need for marketing and ease of recognition all over the world.

After the takeover of Pharmalgen and the changes to ALK's organisation, Chr. Hansen invested further capital by means of a DKK 25.5 million share issue, which brought the total share capital to DKK 27.5 million. Turnover almost doubled to DKK 57.2 million in the financial year 1986-87, and profits tripled to DKK 13.2 million after tax – the same amount as the total turnover just three years previously. This was a striking financial turnaround, and one that was also reflected in a positive net equity of DKK 40.6 million.[53] The takeover of the Pharmalgen line also had wide-ranging consequences in another way. It had been agreed that the production of the Pharmalgen products would gradually be transferred to Denmark over the next couple of years, which would necessitate new and bigger production facilities. The laboratory was already growing too big for Ved Amagerbanen 23, where it was also becoming increasingly difficult to live up to the demands placed on production by new technology and by the authorities in Denmark and abroad (including the FDA).

In addition to this, conditions at the address had become unsafe after a Danish motorcycle gang, Bullshit, leased a neighbouring property. The bikers' general demeanour (not to mention quarrels with their rivals, the Hells Angels), led to fears that the area would become the focal point for clashes or even full-scale gang warfare.

The decision to find new premises had been made even before the takeover of the Pharmalgen line. In November 1987, along with Chr. Hansen, which was similarly inhibited by antiquated facilities, ALK moved practically all its activities to brand new buildings in the Hørsholm Research Centre, later to become DTU Science Park. This area had been earmarked for research and the dissemination of the results of research, and a ban had been placed on factories. ALK was

A new office building in Hørsholm was built in 1998. The building goes by the name 'building 5'.

Laboratory work with sucking hose, Annette Giselson, 1980s.

granted an exemption, however, because its production facilities could be compared with laboratories in other companies, and because production was of very small volumes. FDA approval of the production facilities in Hørsholm was granted in autumn 1988.

ALK held on to its premises at Ved Amagerbanen 23 for a while, partly because they were still FDA-approved and partly because, while the move to Hørsholm was underway, ALK had embarked upon a partnership with the American company Ciba-Corning to develop a new method of testing patients for allergy on the basis of blood tests. Ciba-Corning (later Bayer Diagnostics) worked with a technology that used glass or magnetic particles to bind proteins. The partnership resulted in the introduction of Magic Lite SQ, a brand new, *in vitro* diagnostic product line, onto the European market in 1989-90. The line consisted of reagents in an analysis kit that was sold to clinical laboratories with a special measuring instrument. It was later marketed globally and formed the basis for a separate business unit for blood-test-based diagnostics for allergy.[54] Despite its scientific success and high quality, the management were forced to close down the business unit in 2006 as Bayer Diagnostics had been acquired by Siemens Medical Solutions, which produced a competing product for blood-test-based allergy diagnostics that was already the market leader with a far larger market share.

The ALK companies

Not only ALK, but also Chr. Hansen as a whole was enjoying a positive period. If progress was to continue, however, major investment would be needed - too major to be raised through the existing ownership structure alone. So, in November 1989, the Lundbeck Foundation purchased 93% of the ordinary shares in Chr. Hansen, and committed itself to raising additional capital in the future. In a sense, the company had come full circle, with ALK owned by the Lundbeck Foundation once more, albeit indirectly.[55]

Shortly before the takeover, Chr. Hansen had changed the structure of the company by organising its three business areas into three 'line activities' under a holding company that handled the overall management of the group as well as the ownership of its other companies. The three-line activities were: the CHL companies, which developed and supplied ancillary materials and special products for the food industry; the CHBS companies, which developed and supplied biotechnological products for agriculture; and, finally, the ALK companies.

Despite this ownership structure, in reality the ALK companies were run as a single group centred around the Allergological Laboratory. ALK was once more under the Lundbeck Foundation's ownership and control, but due to its position within the Chr. Hansen group and the new organisational structure, the Lundbeck Foundation now constituted a source of financial support for the continued extension of the company's international position – and the company already had an important acquisition in its sights.

ALK-Abelló is formed

In the late 1980s and early 1990s, ALK occupied a strong position in the USA and was market leader in Scandinavia and central Europe. Yet the company's presence was almost non-existent in Southern Europe, despite collaboration with local distributors in Italy and Spain. One of the many reasons for this was the dominance of the Italian-owned Spanish company, Alergia e Inmunología Abelló S.A. With its headquarters in Madrid and subsidiaries in Italy and Germany, the

company was not only dominant in Spain and Italy but was also ALK's strongest competitor in the European market in general. Unlike Pharmacia, Abelló was purely an allergy company, with an annual turnover in excess of DKK 200 million – higher than ALK's DKK 173 million.[56]

As early as 1989, Engel and Budolfsen had learned that Abelló was to be put up for sale by its Italian owners, the powerful Ferruzzi Group, which was embroiled in a financial and management crisis at the time. If ALK were to purchase the Spanish company, it would solve its southern European difficulties in one fell swoop. Even though it was a large mouthful to bite off, even for Chr. Hansen, contact was established with Ferruzzi to explore the potential for an acquisition. Initial discussions ended negatively, but renewed contact in 1992 resulted in a purchase agreement. To get there, however, Engel and Budolfsen had to threaten to acquire other companies in order to penetrate the southern European markets and compete with Abelló.[57]

Abelló was purchased on 1 September 1992 for DKK 305 million, which was financed by a Chr. Hansen share issue. It was a major investment but helped more than double ALK's turnover to DKK 396 million in the financial year 1992-93, and increased the workforce from 228 to 475.

The acquisition of Abelló created the biggest allergy vaccine company in the world. Abelló did not just provide access to the Italian and Spanish markets, but was a good buy in general. The company was efficient, it was developing favourably, its products were of high quality and its production facilities were modern. Despite cultural differences, Abelló and its staff also had the same fundamental values as ALK, focusing on development, quality and customer information – in other words, the chemistry was good.

Essentially, the Spanish company continued as before, marketing and selling its own products separately and distributing ALK products in Spain. In time, close collaboration developed between Abelló and the other ALK companies in order to exploit synergies, especially in production and research.[58]

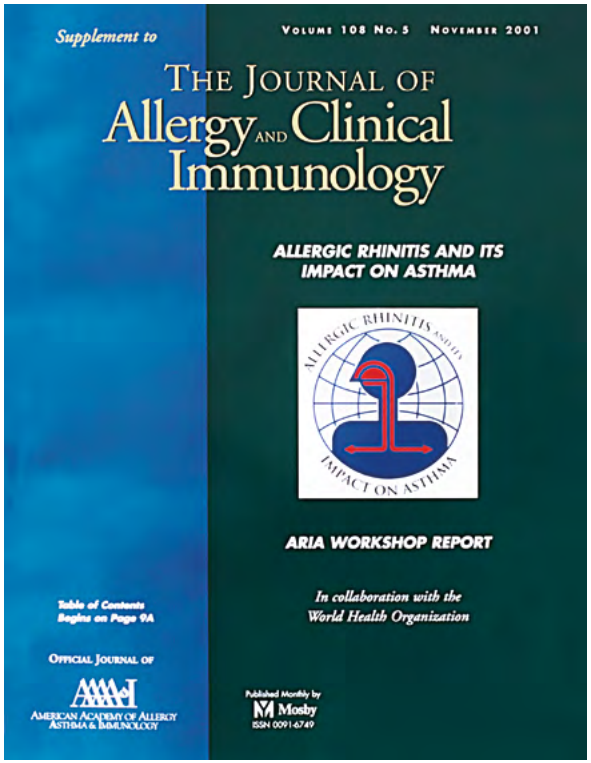
The competitor Abelló was acquired in 1992.

The combination of the two companies' independent activities, as well as their close collaboration within a single Group structure, were emphasised when the title 'the ALK-Abelló companies' was used for the first time in 1995. The change was completed in 1997, when the two parts of the group both officially adopted the name ALK-Abelló.

4.

Out of the niche

In 2001, The World Health Organisation publishes the ARIA report, recommending allergy vaccination.



The creation of ALK-Abelló in 1992 did not end its ambitions of further growth and internationalisation. Shortly before then, its position in the USA had been bolstered by the acquisition of the Californian, FDA-approved company, Berkeley Biologicals Inc., and the company's strategy was now to continue the expansion and strengthening of its international position, not only in existing markets but also by moving into a number of new countries. In the long term, it had China and the rest of Asia in its sights in particular, but the contours of new markets were also beginning to appear in central and eastern Europe, after the fall of the Berlin Wall and the collapse of the communist regimes.[59]

As the 1990s progressed, however, it became increasingly obvious to ALK-Abelló that all the international expansion in the world would not change one fundamental fact: to a great extent, allergy vaccination was categorised as a niche treatment produced exclusively for allergy sufferers who were relatively heavily affected by their allergy, had access to treatment by an allergy specialist and were sufficiently motivated to embark upon a course of treatment that was based on thirty to forty injections at a doctor's surgery over a three-year period.

To make any meaningful change to this situation, ALK-Abelló had to fight on two fronts: firstly, to make the positive effects of allergy vaccination more widely acknowledged by better documenting its efficacy; and secondly, to develop new, more user-friendly vaccine methods. Both would require massive investment in research and development.

Recommended by the WHO

Initially, the documentation of the long-term effects of allergy vaccination was accorded priority. In 1992, ALK-Abelló launched an international research project, the Preventive Allergy Treatment study (PAT), in collaboration with leading European immunologists. The project revolved around the scientifically-based hypothesis that immunotherapy provided early in the course of an allergy could slow down – and possibly completely halt – the allergy; and, especially, that it would be able to prevent the common progression from allergic hay fever to allergic asthma. A total of 205 children with hay fever from five European countries were vaccinated for three years. The long-term effects, including the incidence of asthma, were then to be quantified after five years and ten years. The children were also given preparations to treat the symptoms, as was a control group of children who were not vaccinated, to provide a basis for comparison.

Other research projects were started as well, both under the auspices of ALK-Abelló and independent of the company, and the first results of these began to appear from the mid-1990s. Scientific studies underpinned the hypothesis that early vaccination treatment could slow down the onset of allergy – and prevent the development of asthma. Rather more critically, it was also documented that the treatment retained its effects for at least six years after the vaccination programme had stopped. A continuation of these studies later showed that the effect of ALK-Abelló's vaccines lasted for more than a decade.

All these endeavours to collate clinical documentation about the positive effects of allergy vaccination were definitively crowned when the UN's World Health Organization (WHO) officially rubber-stamped and recommended the treatment method in May 1998. This was done in what is known as a position paper written by the world's leading allergologists. The position paper stated that specific allergy vaccination was the only form of treatment that targeted the source of allergy and was, therefore, capable of influencing the actual progression of the disease, and not just relieving the symptoms.[60]

At the same time, the first results emerged from PAT, the children's study that had started in 1992. These not only confirmed the long-term effects of allergy vaccination but also revealed that only half as many of the children in the study developed asthma as otherwise would be expected. A number of international scientific journals published studies confirming the long-term effects of allergy vaccination, including the New England Journal of Medicine, in which an editorial recommended vaccination against allergy. European patient organisations were also recommending it to an increasing degree.[61]

A highlight in terms of documentation came in November 2001 when WHO published the ARIA report – Allergic Rhinitis and its Impact on Asthma – written by a working group of 37 leading allergologists from all over the world. The report was an important milestone in the understanding of the connection between allergy and the development of asthma, and showed that 80% of all asthma cases in children were due to allergy, while for adults the figure was over 50%. The report, which included a recommended programme for diagnostics and the treatment of patients that included vaccination, was later issued in shortened form as a WHO pocket guide to doctors and therapists all over the world.

Pangramin SLIT (sublingual immunotherapy) launched in 1990.

Need for user-friendly treatment

Despite the scientific recognition, documentation and recommendations from WHO, and despite the fact that enormous numbers of people were afflicted with allergy, with the numbers growing all the time, only 5% of all diagnosed sufferers, at most, were being treated with vaccinations in the 1990s. By far the biggest allergy market was for products that relieve symptoms, typically antihistamines or steroids. Even though these preparations only relieved the symptoms and did not alter the basic allergy, they could be taken easily in the form of pills or a spray and offered patients instant relief. Many of them could be bought over the counter in pharmacies, while specific immunotherapy meant committing to long-term treatment by a specialist and regular injections over three years. This presented ALK-Abelló with a challenge, which it took up in the mid-1990s when it began work on making immunotherapy easier to use and, therefore, more attractive to a larger number of patients.

The best possible outcome would have been to develop a simple treatment that could be prescribed by allergy specialists and other doctors for patients to take at home. If ALK-Abelló succeeded in developing such a method of treatment, the potential would be huge. Not only would it strengthen ALK-Abelló's position in existing markets for allergy vaccines but it would also open up opportunities for the company to break out of the niche it occupied in the total global market for allergy treatment and allow it to commence battle with the dominant medicines that merely relieved symptoms. The question was how and where to begin. In fact, the solution was right in front of them.

The southern European connection: sublingual immunotherapy

Where ALK had always focused on injections, Abelló had been offering its customers in Southern and Central Europe a different method since 1990 - sublingual (under the tongue) immunotherapy (or SLIT). Abelló was the First allergy company in the world to offer vaccination in this form, i.e., a course of treatment consisting of drops under the tongue. Other than the means of application, the process was similar to that of the traditional injection treatments.

The first experiment in giving allergy vaccinations by mouth had been conducted in Germany and Switzerland in the mid-1970s. The results had been disappointing because gastric acid destroyed the allergens and annulled their effects. In Italy, allergy specialists were unable to drop the idea completely and in the years that followed, doctors and patients began to experiment with vaccines that had been designed for injection. Instead of getting them to swallow the vaccines (and inducing gastric acid), the doctors dripped the vaccines under patients' tongues to affect the many receptors there that are directly connected with the immune defence system. Abelló's Italian researchers soon discovered that this form of treatment seemed to work, but company HQ in Madrid was highly sceptical. It was not until 1990, after several years of Italian pressure, backed up by clinical studies and by the strong determination of Dr. Silvano Parmiani (the former Scientific Director of the Italian subsidiary) that the Spanish gave the green light for the launch of the first allergy vaccine product designed specifically to be dripped under the tongue.

Competitors quickly followed suit, and drop-based allergy vaccination became increasingly widespread, at first mainly in Southern Europe, but over time in Germany, Austria and the Netherlands, too. In these markets, it was possible to market the SLIT products as unregistered medicines produced for individual patients under the responsibility of the prescribing doctor. This 'named patient' principle is still more or less unknown in northern Europe, with the historical exception, interestingly enough, of the Allergological Laboratory, which used this method of prescribing in its early years.

ALK was even more sceptical about SLIT than Abelló had been – more so because it had not been involved in its development, which had been ongoing since the initial experiments in the 1970s. The Danes did not really appreciate the potential of sublingual immunotherapy, either at research or board level. The Danish acquisition of Abelló in 1992 meant that, for some years, not enough money was earmarked for research or clinical trials to document the effects of SLIT, with all the funding directed towards further clinical documentation of injection vaccines instead. As a result, the smaller-scale clinical studies being conducted by their colleagues in southern Europe appeared lightweight compared with, for example, the PAT project and published articles in leading journals like the New England Journal of Medicine.

The stagnation in the global allergy vaccine market and the growth of the SLIT treatment south of the Alps eventually galvanised ALK-Abelló's Danish management, however, and in the late 1990s it launched three minor clinical trials with drop-based treatment, in Britain, Germany and Denmark. Characteristically, they chose to use Danish-produced allergen extracts rather than southern European ones; and, although the studies were officially intended to study the output of sublingual immunotherapy, the project was designed so that, in the event of negative results, it could be used to exclude drops once and for all as a useful alternative in the development of new methods of treatment.

It did not turn out quite like that, however. The results were collated in 1999-2000 and, although not unequivocal, they nevertheless confirmed what had been indicated by the southern European studies: that there was a quantifiable effect. They also found that the form of treatment had to be adjusted and refined, however, in order to achieve better results.

In other words, there was considerable evidence to suggest that there was a future in allergy vaccination under the tongue as a form of treatment, and that ALK-Abelló would be well advised to invest far greater resources into a treatment that was clearly preferred by increasing numbers of patients, instead of focusing solely on authoritative documentation of the benefits of injection vaccines.

Drops in single-dose packages

While management in Hørsholm was still deliberating about whether drop vaccines were the future for the company, work was already progressing in Spain to refine the SLIT products. It was not all that easy for patients to make sure they received the proper dosage by counting drops with a traditional dropper, so competitors had started to look at alternatives in the form of sprays or new pump mechanisms.

The Spaniards planned to meet the challenge by introducing a brand new, drop-based product supplied in small, single-dose plastic containers. Bottles would be replaced by these single-dose droppers, which would make treatment easier and dosage safer. On their own initiative, the Spanish launched a documentation and development programme, which included clinical trials and studies of possible packaging methods and production facilities. Their work with single-dose droppers was no secret, but it did not attract a great deal of attention among ALK-Abelló's management in Denmark. Another Spanish initiative did, however - although it took some time.

In January 1999, Domingo Barber, the Spanish director of research, wrote in an email to group management in Hørsholm that he had been thinking about 'a tablet as an alternative to SLIT'[62]. The idea had occurred to him following a conversation with an employee in Madrid, who was receiving treatment for neck pain in the form of rapidly soluble tablets that were placed under the tongue. This could be the solution to a problem that had been occupying Domingo Barber – and indeed, all of ALK-Abelló – for some time: how to facilitate the rapid, efficient and controllable absorption of active ingredients through the mucous membranes under the tongue, while at the same time packaging the treatment in an easily recognisable form that would win the trust of both patients and doctors.

The email failed to elicit any reaction, however. In Hørsholm, the group and its researchers were temporarily focusing on a new, needle-less injection technology. Five months later, Barber sent another email, this time to the British company RP Scherer Ltd. This was the company behind the technology for producing fast dissolving tablets - the same technology that had been used to produce the painkilling tablet taken by Barber's colleague for neck pain. Barber told them of

The World's first sublingual allergy vaccine in single-dose containers, SLITone, launched in 2003.

his interest in developing a new allergy vaccination product based on the British company's technology. It was the start of an important partnership.[63]

As so often happens in medical science and pharmaceutical development, a coincidence had provided the catalyst for the development of perhaps the biggest discovery within allergy vaccination since Henning Løwenstein's SQ technology. Having given up on the development of the needle-less injection technology, this time, Hørsholm did react, ordering a reorientation of ALK-Abelló's product line towards a focus on tablets. And the reorientation did not stop there but extended to the very nature of the company and its understanding of itself.

Reorientation gathered pace on 1 March 2000 with changes to the group management, Jens Bager replacing Elsebeth Budolfsen as CEO and Torbjørn Bjerke succeeding Henning Løwenstein as EVP of Research and Development. Bjerke had arrived at ALK-Abelló the year before and from the start had been an energetic advocate of transforming the company into a developer of new registered phar-

Jens Bager, CEO from 2000 to 2016.

maceutical products. Supported by Chr. Hansen Holding's group management, with CEO Erik Sørensen at the forefront, a massive effort would now be made to transform ALK-Abelló from a niche-based producer of high-quality allergy vaccines into a bona fide pharmaceutical company, in which product development would be directed towards supplying allergy vaccination to a far greater number of sufferers.

Following the shift in strategy, many principal members of staff and new researchers with experience from the pharmaceutical industry were recruited.

SLITone or GRAZAX or both?

Prioritising the development of a brand-new form of treatment was key to the strategic reorientation. The treatment would combine the best attributes of drop vaccines (their user-friendliness) with those of injection vaccines (their wide-ranging clinical documentation and status as registered medicines). A product such as this would have the potential to lift allergy vaccination out of its niche and make it widely accessible.

In terms of business and treatment, tablets were the obvious choice of product. They would inspire confidence in patients and doctors alike, and be recognised by the many allergy sufferers who already used antihistamines to relieve their symptoms. Only a very fast dissolving tablet would allow its content to be ingested under the tongue instead of in the stomach. RP Scherer's technology was the obvious choice.

The reorientation was announced in Chr. Hansen's annual report for 1999-2000 and officially launched on 27 April 2001, when ALK-Abelló announced it had plans in the pipeline to develop four tablets for allergies to grass pollen, house-dust mites, birch pollen and ragweed pollen. The latter was intended for the American market in particular, where ragweed had become one of the biggest sources of hay fever.

To move this development forward, a major international clinical development process would have to be implemented, which would necessitate major financial investment. The project was, therefore, predicated on the goodwill of the Lundbeck Foundation and Chr. Hansen, both of which would have to be prepared to cover ALK-Abelló's losses for several years while expensive clinical studies were conducted.

At first, the full focus was directed towards the development of a tablet against grass allergy – this was later to be given the name GRAZAX. Because all the available resources were directed towards the development of tablets, a halt was called on work to develop drop vaccines.

Barely a year after the starting gun for tablet development had sounded, however, the management in Spain were summoned to a crisis meeting in Hørsholm, where they were told that there was an alarming situation in the drop vaccines market. While ALK-Abelló had been pouring all its development resources into the time-consuming development of tablet vaccines as registered medicines, its competitors in southern and central Europe had quietly been getting on with launching new, user-friendly drop products on the market. As predicted, these inventions were based on pump mechanisms rather than the traditional droppers still being used by ALK-Abelló. And because of the drop vaccines' status as unregistered medicines, ALK-Abelló's competitors were able to launch new products on the market at regular intervals, while ALK-Abelló had to wait for years before launching, while they ran extensive clinical studies with the tablets. Even then, they had to go through prolonged registration processes with the authorities.

Clearly, ALK-Abelló's exclusive concentration on tablets could lead to a crucial loss of market share in the rapidly growing market for drop vaccines. The message to the Spaniards was unambiguous: give us a new drop-based vaccine product that is even more user-friendly than

the competition's and launch it within the year. Luckily, the Spaniards still had their nearly-finished development plans for single-dose drops in a drawer. They promised to meet the deadline.

With full financial and organisational support from Hørsholm, the Spanish succeeded in launching (in just one year, as promised) the first single-dose, drop-based allergy vaccination product, under the name SLITone. Even though most of the development work had already been done, both clinically and in terms of production, it had taken an enormous effort, especially from the Spaniards, to get the product ready so quickly. When SLITone hit the market, it raised not only ALK-Abelló's market share but also its earnings. The company continued to refine tablet-based products, too, and these were to be its ticket to the future.

International launch of SLITone in 2003.

‘The most important meeting in ALK’s history’

On 26 November 2001, the first grass allergy patient placed a GRAZAX tablet under his tongue in a clinical trial. In a pact with history, the first ‘Phase I’ trial of the grass allergy tablet was in progress at the Rigshospital’s allergy clinic – not far from the laboratories where Baagøe and Barfod produced their first allergy extract 80 years before. The trial was preceded by pre-clinical development in Hørsholm and at RP Scherer, where the active ingredients in the grass vaccine were adapted to the new freeze-dried tablet technology.

The trials at the Rigshospital produced the promising finding that GRAZAX was a safe form of treatment in all three dosages used. The conclusion was therefore that a new and much larger international clinical trial should be launched. The international trial, which was called Prograss, was intended to show for the first time whether there was a measurable effect on patients’ allergy symptoms and use of normal symptom-reducing medication. And hopefully show an effect dependent on the dose. This would establish the crucial proof of concept and show that a new type of treatment actually worked in practice.

The world’s first registered tablet-based allergy vaccine, GRAZAX, launched in 2006.

The Prograss trial was to lay the foundations for international registration of GRAZAX, so it was designed on a hitherto unheard-of scale for an allergy vaccination. The trial was to include over 850 patients attached to 57 allergy clinics in seven European countries plus Canada, and would be conducted to the highest standards of clinical documentation. Clinical trials of this magnitude are very expensive to run, so it was crucial to secure financial support, which emerged on 23 October 2002 when ALK-Abelló presented a new international partner to develop and market the tablet vaccines, the US pharmaceutical giant Schering-Plough.

The Board of Management called a press conference in Hørsholm, and there was confidence from all sides that Schering-Plough, whose antihistamine, Clarityn, was then one of the world’s best-selling medicines, had the necessary stock market position and experience in the allergy field to make a global success of allergy vaccines in tablet form.

The agreement was also a welcome endorsement of ALK-Abelló’s strategy of developing tablet-based vaccines, which had previously met with a skeptical response from both allergologists and exchange analysts, and which had cost Chr. Hansen at least DKK 600 million over the past three years.

The agreement assured ALK-Abelló of an immediate payment of USD 6 million (DKK 45 million), and most of the costs of future clinical studies, including the Prograss trial, would be paid by Schering-Plough. The agreement also involved milestone payments to ALK-Abelló later in the process, and Schering-Plough was to pay fees to ALK-Abelló once the products came to market. The income could run to DKK 1 billion in all.

All eyes were then on the 2003 grass pollen season, when treatment of the patients in the Prograss trial was to start. The results could well make or break the strategy around tablet vaccines and with it the remaking of ALK-Abelló as a modern drug company with its own facilities to develop new pharmaceutical products. The agreement with Schering-Plough also gave the Americans the option to decide at the end of the Prograss trial whether they wanted to go on working with the Hørsholm firm.

The tension was dissipated when the clinical findings appeared at the start of November 2003 – and they were not uniformly encouraging. ALK-Abelló had to acknowledge that the trial had not achieved its primary endpoint, which was a statistically significant reduction in allergy symptoms throughout the grass pollen season. On the other hand, it had achieved the other endpoints relating to reduced use of symptom-reducing medicines and enhanced quality of life for the patients.

Nevertheless, the trial had formally failed, which led to 'the most important meeting in ALK's history,' as the company's present Chairman remembers it. The meeting took place in ALK-Abelló's research and development division, and was also attended by Anders Hedegaard, who was then sales and marketing director.[64]

The atmosphere was tense, but when they started to dissect the data, it emerged that the patients who had started treatment at least eight weeks before the start of the pollen season had experienced the desired reduction in allergy symptoms. So, the trial had resulted in a clinical proof of concept, and ALK's new director of research, Henrik Jacobi, then travelled to the USA to present the results to Schering-Plough and explain why ALK still believed in GRAZAX. However, since the two companies had signed the agreement, all of the US top management had been replaced. Schering-Plough was hard-hit by the expiry of the patent for its top-seller Clarityn and was going through a general downturn in sales. In view of this, the new management was not prepared to go further with GRAZAX and discontinued the collaboration.[65]

So, when Chr. Hansen issued a company announcement in mid-December 2003 to the effect that the Prograss trial had produced a documented proof of concept, this was accompanied by the news that Schering-Plough had withdrawn from the partnership.

The reaction from investors was immediate, with Chr. Hansen's share price falling before recovering some of its loss the day after.

The analysts explained that, while ALK had obtained the desired proof of concept, Schering-Plough's cancellation of the partnership had created uncertainty as to the commercial potential of GRAZAX.

So there was both good and bad news, and investors and analysts split into two camps: 'pessimists and optimists,' as Nordea Securities wrote.[66]

Nordea Securities itself was among the optimists and thought that the shares were undervalued, as did asset manager Gudme Raaschou, who stuck to his 'buy' recommendation, while Danske Securities went as far as to raise its recommendation from 'hold' to 'buy'.[67]

On the other hand, asset manager Alfred Berg advised reducing holdings of Chr. Hansen shares, while Sydbank Markets stood by its existing 'sell' recommendation.[68]

The analysts were thus far from unanimous in their assessment; they all continued to believe in GRAZAX after the proof of concept, but also felt that ALK was in a complex position without its US partner.

The senior management and directors of Chr. Hansen and the board of the Lundbeck Foundation still had faith in GRAZAX and confidence in the management of ALK, and preparatory work for registration continued unabated.

To the finish line alone

There was disappointment within ALK-Abelló at Schering-Plough's decision, but this did not cause the company to abandon its efforts to register and market GRAZAX. Instead, it decided to proceed with the submission of a European patent application, while seeking out new partners in the USA and Japan.

To support European registration, the company decided to kick off fresh clinical trials focusing on the dose that produced the best results in the Prograss trial – and with treatment starting at least eight weeks before the pollen season.

However, it did not intend to await the results before submitting an application – instead, the company resolved to submit a registration application for GRAZAX to the Swedish medicines authorities as

At the end of September 2006, 27 European medicines authorities endorsed the Swedish authorisation of GRAZAX.

quickly as possible, based on the Phase I studies and the large-scale Prograss trial. They then planned to send data from the new clinical trials to the Swedish authorities while they were processing the application.

Sweden was chosen because the country had a strong tradition in the field of allergy vaccines, and because the great credibility enjoyed by its health authorities would help later when an authorisation was to be adopted by the other European authorities under the EU's 'mutual recognition' procedure.

In April 2004, Henrik Jacobi therefore travelled to Uppsala to present the data from the Prograss trial to the Swedish Medical Products Agency; the Swedes then agreed to start processing the application and, around midsummer 2004, ALK sent the first batch of registration documents to Uppsala. At the same time, 114 patients in Denmark and Sweden were already well into their GRAZAX treatment in the 'GT-07' trial, which was the first major follow-up study after Prograss.

The treatment started as planned at least eight weeks before the grass pollen got into the air, to give the patients' immune systems time to assimilate the grass allergens in GRAZAX before the effects from nature took hold. The results did not disappoint, as the patients experienced reductions in their symptoms and in their consumption of symptom-reducing medicines which were right up with the biggest trials carried out on injection-based allergy vaccines. These very promising results were confirmed in October 2005, when the results from the much larger Phase III trial, GT-08, appeared, covering more than 630 patients in eight European countries.

As the registration material sent to the Swedish Medical Products Agency grew and grew, it was a busy time in ALK-Abelló's departments for clinical research and regulatory affairs, with fresh documentation to be submitted and clarifying questions to be answered all the time.

Time passed, and everyone's patience was stretched to breaking point, but on 14 March 2006 came the answer they had been waiting for when the Swedish authorities approved the world's first tablet-based allergy vaccine, GRAZAX.

This was followed by the mutual recognition procedure across the EU and, at the end of September 2006, 27 European medicines authorities endorsed the Swedish authorisation of GRAZAX. The launch could begin, and before the year was out, GRAZAX was available for the first time in one of ALK-Abelló's largest markets, Germany.

Ahead lay the efforts by management to find partners in Europe and the USA. They also contacted the company's arch-competitor, Stallergenes in France, to look into a possible merger. However, these soundings came to nothing, and the company entered into two major agreements in Europe and North America to develop and market GRAZAX.

After the convincing clinical results and granting of European authorisation, ALK-Abelló was able to sign an agreement with the Italian Menarini Group as early as December 2006 to sell the tablet vaccines in the European markets where ALK-Abelló was not sufficiently well-represented.

The results from the clinical trials and the European authorisation made an impression in the USA too, and to many people's surprise, the former partner Schering-Plough returned as partner for North America. The new management of the group had reconsidered the tablet vaccines, and at the beginning of January 2007, the US company entered into a new agreement with ALK-Abelló. With a total contract value of almost DKK 1.5 billion on top of future royalties from sales, the new agreement was far more lucrative for ALK-Abelló than the first.

GRAZAX was on its way onto the global medicines market, and the first crucial milestone was passed in the development and marketing of a diverse portfolio of tablet vaccines against allergies.

14 March 2006 the answer everybody had been waiting for arrived: approval from the Swedish authorities of the world's first tablet-based allergy vaccine.

5.

Tablet strategy and new partnerships

Foundation ownership and exchange listing

When the Swedish authorisation for GRAZAX took effect, ALK-Abelló had become an independent company once more. The Lundbeck Foundation had put the ingredients business in the Chr. Hansen Group up for sale in November 2004, but wanted to retain ALK-Abelló, which came as a great surprise not only to stock exchange analysts but also within ALK.

Earlier in the year, ALK-Abelló had applied for approval of GRAZAX in Sweden on the basis of the initial registration materials, and according to the analysts, the expectations for GRAZAX were the driver behind the sharp rise in Chr. Hansen's share price. At the same time, surprisingly good sales of SLITone were seen as the main reason why Chr. Hansen adjusted its profit forecast upwards.[69]

The Lundbeck Foundation therefore opted to invest in ALK-Abelló and sold the ingredients business to the French investment fund, PAI Partners, at the end of April 2005. Chr. Hansen Holding was then merged into ALK-Abelló on 13 December 2005, with ALK entering a new life as a stock exchange-listed company with the Lundbeck Foundation as majority shareholder.

The combination of controlling foundation ownership and stock exchange listing was (and is) an ownership model unique to Denmark, where it encompasses many of the biggest companies. The Lundbeck Foundation owned 35.2 per cent of the shares in ALK-Abelló, with the rest available for trading on the Danish Stock Exchange. The Lundbeck Foundation still held the majority of the votes however because its ownership covered all 'A' shares, which made up just 9.1 per cent of the capital but carried 10 votes each, while the 'B' shares had a single vote each.

Like most commercial foundations in Denmark, the Lundbeck Foundation is not-for-profit, so a proportion of the dividends must be used for non-profit or charitable purposes. The Lundbeck Foundation particularly supports medical research, and some of its dividend income from ALK-Abelló is therefore used for research that could lead to the development of new treatment methods and medicines.

The Lundbeck Foundation provided ALK-Abelló with stable ownership with the emphasis on long-term earnings, which was in line with the company's goals. However, neither the foundation nor the company could – or wished to – ignore the interests of the other shareholders, so there was a big focus on earnings, the share price and dividend payments, a new discipline for the company after operating as a subsidiary of the Chr. Hansen Group since 1979.

Financially, ALK-Abelló was well-consolidated as all of the development of GRAZAX was already paid for, and the proceeds from the sale of the ingredients business were split between the shareholders and ALK-Abelló. The company was then independent without any debts and with liquid assets of DKK 600 million – and a new groundbreaking allergy treatment on its way to authorisation and marketing. The number of employees was 1,227.

Great expectations for GRAZAX

When it became independent, ALK-Abelló had been making steady progress since 2002, and in its first full financial year of 2005/06, the company posted a growth in sales of no less than 22 per cent, of which 9 per cent came from organic growth and the rest from the acquisition of the French allergy company Allerbio S.A. Revenue came to just under DKK 1.5 billion, and operating profit was DKK 276 million.

It was GRAZAX that would bring ALK-Abelló properly out of Chr. Hansen's shadow – and more than that: 'Without comparing it with Novo Nordisk or Lundbeck, ALK-Abelló could become one of Denmark's new medical flagships. The prospects are that good,' said the company's Chief Executive Jens Bager, referring to the two biggest Danish pharmaceutical firms, with annual revenues of DKK 34 billion and 9 billion respectively.

Research and Development Director Henrik Jacobi made no secret of his great expectations either: 'The problem is getting hold of enough raw materials – how many meadows are there to mow?' he asked rhetorically – well aware of the answer, which was that the company had already secured sufficient supplies of raw materials.[70]

Henrik Jacobi, Executive Vice President, Research & Development, from 2003-2023.

There were great expectations for GRAZAX in the Lundbeck Foundation too. The Chairman Arne V. Jensen, who had been chair of Lundbeck and knew the pharmaceutical industry from the inside, declared that 'if ALK manages to create a new market for allergy tablets, the sky's the limit.'[71]

Confidence in GRAZAX was also high among the analysts: 'Danish allergy giant in the melting pot,' read the headline in the influential Danish business paper *Børsen*, suggesting that GRAZAX could take ALK-Abelló's revenue above Lundbeck's. *Berlingske Tidende* struck the same tone with the headline 'ALK on course for a pharmaceutical adventure.'[72]

Expectations were equally high everywhere, and the immediate market potential was also huge. Around 5 million people in Europe were thought to have moderate to severe grass allergy, and if ALK-Abelló could reach 20 per cent of them, the patient group would number 1 million and lead to ten times the existing sales, as the company was currently selling grass allergy vaccines to around 100,000 patients.[73]

The company had a further advantage in that the French company Stallergenes, which was its biggest competitor, was estimated to be two years behind in the development of a grass allergy tablet. ALK-Abelló would therefore have time to establish a strong market position before a rival preparation came on the market. So GRAZAX could quickly generate annual revenues of DKK 10 billion, according to the analysts.

Meanwhile, the chair of the Lundbeck Foundation, Arne V. Jensen, had put his finger on a crucial point, which was that the success of GRAZAX depended on ALK-Abelló being able to create a new market. First of all, allergy patients were very reluctant to enter a three-year course of vaccine treatment with 40-50 injections in all, and although the tablets would strike them as more user-friendly, they were a completely new and unknown type of treatment and would have to be taken daily for three years.

Skeptical assessments were heard from some specialists – partly because, unlike injections, there was no documentation of the long-term effect of the tablets. ALK could not provide this, for good reasons – at least not yet. They therefore said that they would monitor the patients in the large ongoing GT-08 trial, initially for two years after the end of the treatment, in order to document the long-term effect.

There was also an uncertainty factor in that the price of the treatment and the amount of the public reimbursement had to be negotiated with the health authorities in the individual countries. Both factors had a crucial bearing on the amount paid by patients and hence on sales. The price of the tablet treatment was significantly higher than the injection treatment, and apart from the greater comfort for patients, the authorising authorities also had to judge whether this could be justified by the therapeutic effect.

Nevertheless, there was massive optimism within ALK-Abelló, recalls Anders Hedegaard. Unlike the analysts, ALK-Abelló was still reluctant to release concrete forecasts to the wider world but did venture a cautious announcement of expected sales of DKK 100-150 million in 2007.[74]

Few pricing and reimbursement agreements

There was a lot at stake for ALK-Abelló, as it faced not only the launch of a new allergy product but also the introduction of a completely new tablet technology upon which the whole raft of future allergy preparations would be based.

It started promisingly with the initial launch of GRAZAX in Germany in November 2006 after agreement on the price was reached with the country's sickness benefit providers and health authorities, which had decided to reimburse in full. Germany was already ALK-Abelló's biggest market, and as the price of GRAZAX was set higher than expected, expectations for pricing, and hence revenue, in other countries rose accordingly.

However, things turned out differently. As 2007 had a mild pollen season, tablet sales amounted to just DKK 47 million, well below even the most pessimistic expectations. ALK-Abelló itself put the disappointing sales down to the fact that it had proved harder than expected to obtain public reimbursement for the treatment, and the decisions in the individual countries had taken a long time.[75]

The health authorities in six European countries had followed Germany's example and granted full public reimbursement: Norway, Sweden, Finland, the Netherlands, Austria and Greece. Switzerland, which was outside the EU and therefore outside the common European authorisation procedure, also approved the preparation and agreed to reimburse the costs from the public purse, and the preparation was launched at the beginning of 2008.

The UK was a saga in itself, as GRAZAX was granted national reimbursement but it was then left to 150 regional sickness benefit providers to decide on the final amount. As allergies were not a top-priority area of medicine and there was no tradition of allergy vaccination in the UK, the market launch proved to be more difficult than expected, and ALK-Abelló had to adjust its marketing strategy.

In Italy the situation was quite similar, even though the country had an established tradition of allergy vaccination. So GRAZAX was granted national reimbursement there, but it was then up to the regional health authorities to decide on the allocation and amount of the payment, which were still under negotiation. In both Spain and France too, it proved harder than expected to reach agreements on reimbursement, so GRAZAX was not launched in these countries either.

Quite unexpectedly, it was not possible to obtain general public reimbursement in Denmark, where the Danish Medicines Agency

There was a lot at stake for ALK-Abelló, as it faced the introduction of a completely new tablet technology upon which the whole raft of future allergy preparations would be based.

justified its refusal on the grounds that the therapeutic value of GRAZAX compared to the injection-based vaccine was not proven. So, it was not possible to determine whether the higher price was matched by higher therapeutic value, and there was insufficient knowledge of the long-term effect. In exceptional cases, it was however possible to grant individual reimbursement, e.g., in the case of needle phobia.[76]

The refusal meant that Danish allergy patients were actually excluded from treatment unless they paid the full amount themselves. The decision caused resentment within ALK-Abelló as it sent a bad signal to the health authorities in other countries for GRAZAX not to be granted public reimbursement in the company's own home country.

Nor did the company omit to stress in its annual report that authorities in other countries recognised not just the clinical effect but also the socio-economic benefits of the tablet vaccine, which improved patients' quality of life and reduced the number of sick days and the use of symptom-reducing medicines. Moreover, the costs of a visit to the doctor were much less than for an injection-based vaccination, as the patients themselves could take the tablets without medical assistance.[77]

It was small consolation when ALK-Abelló was awarded the Confederation of Danish Industry's product prize for GRAZAX. The prize is awarded each year to honour companies which 'develop exceptional customer solutions.' The citation emphasised that GRAZAX was an 'an innovative breakthrough that will pave the way for new tablet-based allergy vaccines,' and that, along with the benefits to patients, it would 'free up resources in the healthcare sector,' as patients would not need multiple injections from a specialist but could take the tablets themselves.[78]

GRAZAX: The world's best documented allergy vaccine

In parallel with the launch, the clinical trials of GRAZAX continued, both to extend the treatment indication to children and young people and to document the long-term effect. The main results from a Phase III trial of GRAZAX in children were then published in November

Specialist laboratory technician, Jelena Djuricanin, working in ALK's laboratory in Hørsholm, Denmark.

2007. This trial had been carried out in Germany with 253 patients aged five-to-sixteen and showed a statistically significant clinical effect comparable to the results from the development programme for adults, and on this basis, GRAZAX gained EU approval for treating children and young people in November 2008.

ALK-Abelló was also pleased with the progress of the long-term study GT-08, with the publication of data from the first follow-up year in October 2008. This showed that the effect of GRAZAX was sustained after the end of the three-year treatment programme, and blood samples from the patients showed a lasting positive effect on the immune system. In 2009, based on these results, the European medicines authorities authorised GRAZAX as a disease-modifying allergy treatment – a historic milestone not only for the product but also for the tablet technology. In ALK-Abelló's own words, it was now established that GRAZAX constituted 'a fully functioning allergy vaccine' on a par with the injection-based vaccines.[79]

On the other hand, the first clinical Phase III trial in the USA turned out badly because of mistakes in recruiting patients. A large proportion of the patients had only mild symptoms, and as GRAZAX was intended for severely affected patients, the results which were published in November 2007 could not show any clear effect. The reaction from the Danish Stock Exchange was immediate, with ALK's shares falling by 35 per cent from around DKK 1,000 to DKK 630.

The trial was worthless, but Schering-Plough still had faith in the preparation. But it had to wait until the next pollen season for a new study to be carried out, and Schering-Plough also wanted to launch a clinical trial on children. Both were initiated in 2008, but before the results were out, Schering-Plough was bought out in November 2009 by one of the world's largest pharmaceutical firms, Merck, which thereby acquired the North American rights to ALK-Abelló's tablet programmes.

In connection with the takeover, Merck planned to review all of Schering-Plough's research and development projects, and there was concern within ALK-Abelló that the partnership would be dropped: 'There was real pressure on us, because we had to ensure that Merck understood our technology and potential before they started prioritising their development projects,' recalls Henrik Jacobi, who flew straight to New York to meet with Merck's head of development. The meeting took place in a restaurant, where Henrik Jacobi presented the project on his laptop, before taking a taxi to the airport and flying back to Europe after spending seven hours in the USA - three of them in the restaurant.[80]

Merck was persuaded to continue with the project, and when the results from the clinical trial came out early in 2010, they showed the same effect as ALK-Abelló's corresponding trial in Europe. Merck then expected to submit an application for registration in America around the turn of the year from 2010 to 2011.

To complete the scientific documentation, ALK-Abelló launched a large-scale clinical trial in 2010 to run over five years in ten European countries and involving 600 children aged five to twelve. Studies had shown that allergic children had up to seven times greater risk of developing asthma later in life, and the aim of the GAP (GRAZAX Asthma Prevention) study, as it was named, was to investigate the extent to which GRAZAX could prevent asthma developing in children and young people. The company itself expected the study to show that treatment with GRAZAX could reduce the risk of children developing asthma.[81]

All of these clinical trials, with more than 6,000 patients in all, meant that, by 2009, GRAZAX was the world's best documented allergy vaccine. However, it was still taking time to enter into new pricing and reimbursement agreements, especially in southern Europe; Spain came on board in 2008, but it took until 2010 for an agreement to be concluded in France. GRAZAX was then finally available with public reimbursement in all of the major European markets.

An exception was Denmark, where ALK-Abelló submitted a fresh application for general public reimbursement around the end of 2008. Notwithstanding the results from the first follow-up year of the GT-08 study and the EU's recognition of GRAZAX as a disease-modifying allergy treatment, and despite the wishes of Danish allergy doctors and the Asthma-Allergy Association, the Danish Medicines Agency limited itself to a slight easing of the individual reimbursement criteria.

Only after the results from the second follow-up year to the GT-08 were published in early 2010, confirming the long-term effect of GRAZAX, did the Danish Medicines Agency agree, in April 2011, that Danish grass pollen allergy sufferers could use GRAZAX with full reimbursement. This produced a fivefold increase in the number of Danish patients treated with the tablet, from 200 to around 1,000 by the spring of 2012.[82]

Updated strategic plan based on tablets

The disappointing sales of GRAZAX in its first year on the market did not cause the management of ALK-Abelló to slacken its resolve. Instead, in 2008 the Board of Management and the Board of Directors adopted an updated strategic plan, *Focus 2012*, which affirmed the strategic ambition to extend the use of allergy vaccination by introducing new tablet-based allergy vaccines.

The company had been investing heavily in recent years in expanding its research and development activities, as well as strengthening the sales and marketing organisation and increasing production capacity to assure the success of the tablets. Back in 2007 it had launched a three-year investment programme to build a new raw material production facility in Idaho, USA, and a new production line to manufacture tablets at the sub-contractor Catalent in Swindon in the UK, intended to produce tablet-based vaccines for the American market. ALK also started the construction of a new building at Hørsholm, Denmark, so all of the company's Danish employees were now located in the DTU Science Park.

A new building was built in Hørsholm so that all employees in Denmark could be united on the DTU Science Park.

The GRAZAX tablet packaging for the German market.

With the first tablet-based vaccine on the market, the focus moved to the next step, which was to ensure sustained, profitable growth of 10 per cent per year. This would be done by developing and extending the markets for the new tablet-based vaccines where high growth could be expected – while maintaining the growth in the traditional vaccine business.

Alongside the update to the strategic plan, ALK-Abelló introduced a new visual identity and a new logo to replace the existing look from

its earlier affiliation with Chr. Hansen. It also established a uniform global identity for the whole of the group by changing the names of the subsidiaries to tie them to the legal name ALK-Abelló – informally referred simply as ALK – and having them all use the group's new logo instead of their own.

For the moment, GRAZAX was the only tablet-based vaccine, while the next preparation in the pipeline was a tablet-based vaccine against house dust mite allergy, which was in late clinical development. This would be followed by tablet-based vaccines against ragweed and birch pollen allergies, both in clinical Phase I testing. The ragweed vaccine was aimed at the American market, so Merck looked after the clinical trials while ALK handled the process for the birch pollen vaccine.

Despite the key role of the tablet-based vaccines in the strategic plan, there was no stated time frame for submitting applications for approval, let alone expected launch dates. The clinical trials also faced a number of issues which made it hard to announce a definite time frame. For example, unlike other drugs, clinical trials on the pollen allergen tablets could only be carried out in the pollen season, and the results were dependent on its intensity and duration. A mild pollen season produced weak results which could not demonstrate sufficient effect and necessitated a fresh trial.

Another equally crucial issue was that there was no certainty that these costly clinical trials could be financed. Whereas the entire development of GRAZAX had been paid for by Chr. Hansen, ALK itself now had to cover all of the costs of the subsequent tablets. And as substantial amounts were still being spent on trials on GRAZAX, particularly the five-year GAP study which started in 2009, it was unclear whether, when – and to what extent – it would be possible to carry out the clinical trials of the other tablet-based vaccines.

Finally, the experience with GRAZAX had shown that the clinical trials could be followed by a long drawn-out authorisation process for the preparation – and then came the negotiations on prices and public reimbursement in the individual countries.

Particular issues with the house dust mite tablet

One exception to the seasonal dependency of clinical trials was the house dust mite tablet, as this allergy, unlike the other respiratory allergies, is not seasonal but is present all-year-round. However, there were other specific issues in developing the tablet-based vaccine.

House dust mites carry a very large number of allergens, and people with allergies may not necessarily react to the same ones. Right from the start, therefore, two different allergen extracts were to be developed, to be mixed in a particular ratio so as to cover the principal and most widespread allergens. The manufacturing process involved dividing the house dust mite into its different body parts and faecalia, and in the words of Research and Development Director Henrik Jacobi, the allergen extract was 'very difficult to produce.'[83]

Moreover, large amounts of the allergen extracts had to be produced for the clinical trials, as tablet-based treatment requires much greater

Allergens from house dust mites are used to produce vaccines for house dust mite allergy.

quantities than injection treatment. This challenging production process meant that, to begin with, it took a year to manufacture just the necessary amount of allergen extract for a clinical trial, which raised a fresh problem – or at any rate a new headache.

The allergen extracts were produced in Hørsholm, while the tablets were made in Swindon. So the extracts had to be driven to Swindon by freezer truck in the form of frozen drops, but what if the truck went the wrong way, or the cooling system failed? So a second freezer truck was sent out as a backup in case anything went wrong – and an ALK employee went along for the ride, so the drivers did not have to manage any problems on their own. Nothing could be allowed to go wrong, and Henrik Jacobi compared the whole process to 'putting a man on the Moon.'

However, getting the allergen extracts through to the sub-contractor, Catalent, which produced the freeze-dried tablets from ALK's allergen extracts, was not the end of the story – far from it. Early in the process, the tablets started to break up, and nobody knew why until they found out that the allergens – which were digestive enzymes – were breaking down the gelatine in the tablets.

This was a disaster, but a Merck employee attending a meeting with ALK came up with a solution to the problem. This involved mixing the allergen extract with the gelatine immediately before the tablets were freeze-dried. ALK worked with Catalent to implement this solution, which meant modifying one of Catalent's production lines.

Tighter official requirements for evidence and documentation

Notwithstanding the goals in the strategic plan, GRAZAX was the only preparation to achieve the aim of high growth for tablet-based vaccines, as the clinical trials on the other tablets were lagging behind, with none of them reaching competition within the 2012 time frame. The main reason for this was a lack of financial resources due to weak growth and profitability in the core business, partly because of continued disappointing sales of GRAZAX, which was performing well below expectation and fast becoming something of a 'punch in the gut,' as some put it.[84]

It is true that revenue grew to DKK 87 million in 2008, and DKK 162 million in 2010, when GRAZAX became ALK-Abelló's biggest single product. Nevertheless, it fell well below expectations – and after four years was not doing much better than ALK's own expectations for sales of the preparation in its first year on the market.

GRAZAX was a factor in ALK-Abelló's success, as were the injection and drop-based vaccines, and in 2010 the company achieved total revenue of DKK 2,140 million. However, around DKK 100 million came from the purchase of two companies in the USA and the Netherlands, and organic growth accounted for just 4 per cent. The number of employees grew by almost 100 to 1,612 full-time equivalents.

This slow growth should be seen in the light of several factors. On the one hand, continuing prolonged negotiations on reimbursement were still delaying the roll-out of GRAZAX, while the global financial crisis of 2008-2009 had a negative impact, especially in southern Europe, where the price to users of the allergy vaccines was very high, causing many people to defer or reject the treatment altogether. Then there were political measures in Germany and the Netherlands, with lower reimbursement and price caps reducing sales in 2010.

Moreover, the European market for allergy vaccines was changing after the health authorities in several countries started to impose requirements to register the so-called NPP (named patient preparations), which were not registered drugs but used on a patient-specific basis under the auspices of the prescribing doctor. This mainly related to drop-based vaccines.

It was particularly in Germany, the Netherlands, Spain and Italy that the requirements were tightened up to provide for the maximum documentation and quality of treatment. ALK itself was hit by these measures but welcomed the development as it would benefit patients and was in line with the company's own development ambitions to be a pharmaceutical company selling registered products, where the vaccine tablets were identified as the core product.

ALK was already the allergy vaccine producer with the largest number of registered products, and to meet German registration requirements, the company submitted a further 19 applications in 2010 in order to maintain sales in the future. These were for a number of drop-based products plus the recently introduced line of injection vaccines, AVANZ, which allowed a faster increase in dosage and was therefore more patient-friendly.

Together the 19 preparations accounted for around 7 per cent of ALK's total revenue

Partnerships in the USA and Japan

The progress made after the launch of GRAZAX covered all of the company's three regions – northern, central and southern Europe – but it did not manage to launch its allergy vaccines in eastern Europe and Russia, which had been the main reason for entering into the agreement with Menarini in Italy. Even in 2009 the two companies could see that these markets were not mature, and it was agreed to discontinue the partnership at the end of that year. At the same time, ALK took over the activities in Ireland and Greece, where Menarini had introduced GRAZAX.

However, with the company's limited financial and standardised resources, partnerships with other companies remained a key part of ALK's strategy for global distribution of its allergy vaccines. The partnership with Merck also continued as agreed, although it was taking time to submit an application to register the products in the USA.

However, the reason was not sluggishness on the part of Merck, but uncertainty within the company and the registration authorities. Although it was estimated that around 25 million people in North America suffered moderate to severe allergies, particularly to grass, ragweed and house dust mites, there were no standardised and registered preparations for allergy immunotherapy on the market. On the other hand, around 3 million people were receiving treatment with injection-based vaccines produced by their doctors for individual patients from ingredients supplied by ALK and others. These were often so-called vaccine "shots" containing a mix of several allergens, as many patients suffered from multiple allergies at the same time, and the allergologists wanted to be as sure as possible of seeing an effect.

So this was the first time the US medicines authority, the Food and Drug Administration (FDA), had processed an application to register a preparation for allergy immunotherapy. There were then discussions between Merck and the FDA on the registration process and the specific requirements for analyses and documentation, the outcome of which was that the FDA wanted yet another large-scale clinical trial to display less variation in the effect of treatment with GRAZAX than the existing studies.

Merck therefore decided to carry out the biggest ever trial of GRAZAX, including 1,500 patients, with an application for registration expected to be submitted in 2013. Of course the delay was a setback, but it was also a good sign in that Merck's decision showed it was fully committed to the partnership and believed that GRAZAX had real potential in North America.

Meanwhile, Merck's clinical Phase III trials of the ragweed vaccine were proceeding to plan, with expected completion in 2011, while its clinical trials of the vaccine tablet for house dust mite allergy were in Phase II.

At the beginning of 2011, ALK established another significant partnership agreement with a pharmaceutical company – this time in Japan, which was the world's second-largest market for allergy medicines after the USA. The partner was Torii Pharmaceutical Co. Ltd., which marketed a wide range of medicines and had been the only company in Japan producing and selling allergen-specific medicines for the last 40 years.[85]

As in the USA, there were no standardised and registered preparations for allergy immunotherapy in Japan either, so patients were treated with injection-based vaccines made specifically for each individual. The agreement was intended to change this, as it covered the development, registration and marketing of ALK's tablet-based

vaccine for house dust mite allergy and a research and development partnership to produce a tablet-based vaccine for cedar wood allergy.

Up to 30 per cent of the population in Japan suffered from house dust mite allergy – which was seen as a major cause of asthma – or from cedar wood allergy, so there was a great need for a better treatment for both allergies. The agreement also covered one of ALK's injection-based vaccines for house dust mite allergy, as well as diagnostic tools for this.

On entry into the agreement, ALK received an *up-front* payment of DKK 224 million, with subsequent milestone payments to the same amount, plus milestone payments and royalties from sales in Japan when these came on stream. All of the costs of development, registration, marketing and sales would be borne by Torii, while ALK would look after the production and supply of the tablets.

Company acquisitions and purchase of products

Alongside these partnerships, ALK was also strengthening its own international organisation and presence. In 2008, it took over all of the allergy vaccination business from its existing distributor in Canada, Western Allergy Services Ltd., and transferred them to a newly-established subsidiary. The company strengthened its presence in the USA too, with a small acquisition in 2010 whereby it took over the allergy vaccination activities from Nelco Laboratories and integrated them into ALK's American subsidiary.

There were acquisitions in Europe too, as a number of the fifteen-plus different allergy companies marketing NPP vaccines were having difficulty financing the costs of documenting the effect and quality of their vaccines. ALK took advantage of this, taking over the largest allergy vaccine producer in the Netherlands, Artu Biologicals, in 2010 and merging its activities into ALK's Dutch subsidiary. Artu marketed SLIT-drops, and the most important preparations had gained temporary registration through to July 2012. The company's revenues in 2009 ran to DKK 194.2 million, so the takeover made a significant contribution to growth in ALK.

At the beginning of 2011, ALK established a significant partnership agreement with the Japanese pharmaceutical company, Torii Pharmaceutical Co. Ltd.

Along with these acquisitions, ALK made a long-term investment in January 2009, purchasing shares worth DKK 15 million in the French biotech company, DBV Technologies, which specialised in food allergies. ALK-Abelló's Managing Director, Jens Bager, also joined the board of directors of DBV.

This investment enabled ALK to enter into a partnership to develop a promising vaccine for peanut allergy, which is one of the most serious food allergies where patients can suffer very violent allergic reactions – in the worst case, even anaphylactic shock, which can be life-threatening.

DBV Technologies used a radically different technology from ALK, with work on its peanut allergy vaccine based on an electrically charged patch technology which enables gradual uptake of the active vaccine ingredients through the skin. In the autumn of 2010, an initial Phase II clinical trial was launched in France, and another was expected to start in the USA the year after.

In December 2010, ALK therefore invested a further DKK 15 million in DBV Technologies in connection with a share issue. ALK's owner, the Lundbeck Foundation, and other international investors also participated in the new issue, which was to finance the late development phase of the peanut allergy vaccine, which had already been given the name Viaskin.[86]

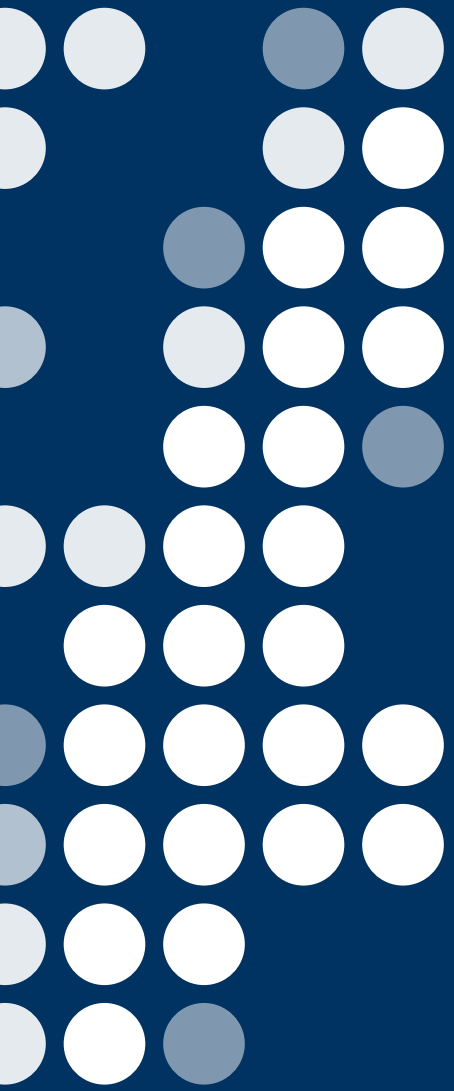
This engagement was on the periphery of ALK's traditional business, as the company had not previously worked on food allergies. On the other hand, it gave ALK insight into a new technology for developing allergy vaccines which it had not used before, and also gave it visibility in potential new markets.

The same was true of an agreement entered into in September 2009 with the US company AllerQuest, which gave ALK exclusive global rights to market a skin test for penicillin allergy, PRE-PEN, which had just been approved by the FDA. PRE-PEN was not a new product but had been on the market for more than 30 years before production stopped in 2004, when the production facilities were criticised by the FDA.

The interest in the product was that it could not only determine whether a patient had penicillin allergy, but also the reverse, as many of the patients who thought they were allergic to penicillin actually weren't. So there was great potential to cut down the use of broad-spectrum antibiotics as a substitute for penicillin and so inhibit the development of multi-drug resistant bacteria.

PRE-PEN was the only penicillin test of its kind and therefore much sought-after, so the next year a group of allergy specialists and doctors founded AllerQuest to take over production. After obtaining FDA approval for new production facilities, the company entered into an agreement with ALK, which became sole distributor – initially in the USA, although there were plans to launch in other countries too.[87]

The partnership with DBV Technologies was not a success, and ALK disposed of its shareholding in 2013-2014 as the peanut project was not developing as had been hoped. Instead, Stallergenes entered into a partnership agreement with DBV Technologies in October 2014 to develop a patch technology to treat birch pollen allergy.



6.

Portfolio of vaccine tablets

The newly-developed adrenaline pen, JEXT, for acute treatment of anaphylactic shock.

Updated strategic plan with clear financial targets

Partnerships and acquisitions of other allergy companies were key components of the updated strategic plan, Focus 2015, which was adopted by the Board of ALK in 2010. Unlike its predecessor, the plan included clear financial targets. Revenue was expected to grow to at least DKK 3 billion in 2015, while the operating profit (EBITDA) should be at least 25 per cent, or DKK 750 million. These were ambitious targets, particularly in light of the market situation in Europe where the company expected modest growth rates in vaccine sales in the coming years, plus the continued political focus on medicine prices and reimbursement, which were to reduce sales by DKK 130 million in 2011 in Germany alone.

However, ALK expected the combined milestone payments from Merck and Torii to contribute up to DKK 500 million in the period leading up to 2015, while the company itself intended to generate the rest through an increased emphasis on marketing GRAZAX and introducing the tablet-based vaccine into new markets. The imminent introduction of the company's newly-developed adrenaline pen, JEXT, for acute treatment of anaphylactic shock, was also expected to contribute. Then there were acquisitions of allergy companies and the purchases of new products and businesses in new areas.

After 2015, the company expected growth in both revenue and earnings to pick up significantly, as the tablet portfolio was expected to be fully developed and complete by that time in Europe, the USA and Japan – except for the tree allergy tablet.

Things also started promisingly, with revenue increasing by 10 per cent to DKK 2,348 in 2011, and operating profit (EBITDA) rising by as much as 41 per cent to DKK 406 million. This exceeded expectations and was mainly down to milestone payments from Merck and Torii totalling over DKK 240 million, which went straight to the bottom line. As expected, vaccine sales grew by 5 per cent with performance driven by GRAZAX, which increased sales by 12 per cent to DKK 183 million, and the new product line, AVANZ, which doubled its sales after being launched in Germany, Austria, Italy and Spain.

So there was every reason to stick to the target for 2015, although the company's new Chairman, the CEO of Novozymes, Steen Riisgaard, who was elected at the general meeting in March 2012, was restrained in his expectations. He described ALK as 'a biotech company rather than an actual going concern,' and although the company still wanted to increase its revenue in the period to 2015, it was only then that it would 'engage both turbochargers' with the expected launch of the new tablet vaccines.[88]

In 2012, however, rather than continued progress there was a setback when ALK experienced its first fall in revenue since the split from Chr. Hansen, albeit a marginal one – a modest DKK 3 million. There were continuing big gains for the GRAZAX and AVANZ product lines, while vaccine sales as a whole produced growth of just 0.4 per cent. Income from the milestone payments from Merck and Torii also fell slightly.

There was worse news for sales of adrenaline pens and diagnostic tools etc., which fell by 11 per cent (as expected). ALK had launched the JEXT adrenaline pen during the year, but it was up against a strong and established brand and, to begin with, the company could not keep up with demand. In the later months of the year, however, sales grew strongly and there were great expectations for the coming years.

The same was true of a new product line of drop-based vaccines, SLIToneULTRA, aimed particularly at France, Spain and Italy, and also launched in 2012. The preparations differed from the existing SLITone in that they were more user-friendly and could be stored at room temperature for up to three months. In the first instance, the product line was launched as 'named patient' preparations.

Simplify, Innovate, Grow

GRAZAX, AVANZ and SLIToneULTRA were projected to be the key growth drivers out to 2015, when the other allergy vaccine tablets were expected to come onto the market. JEXT was also assigned a key role, with targeted sales of more than DKK 200 million by 2015.

ALK therefore maintained its strategic target for 2015 to achieve revenues of at least DKK 3 billion and operating profit of 25 per cent. To support this effort, the company's strategic plan was updated at the end of 2012, extending it to 2016 under the headings *Simplify*, *Innovate* and *Grow*.

Simplify consisted of initiatives to simplify the product portfolio, consolidate production into fewer units and bring a number of back-office functions together in the company's head office in Hørsholm. By 2016, around 60 per cent of the older product portfolio was to be phased out and replaced with new and standardised vaccines.

At the same time, a number of smaller production units were to be shut down and production consolidated into fewer units in Denmark (injection and tablet vaccines), France (drop vaccines), Spain (diagnostics, packaging and distribution), New York (vaccines for North America) and Idaho (raw materials). The production units were also be upgraded to so-called *centres of excellence* meeting the latest quality and safety requirements. Work was already under way in France, with DKK 135 million to be invested in that country alone, including expansion to keep pace with the rising demand and to produce the new SLIToneULTRA preparations.

The business organisation was to be simplified and globalised, bringing IT and financial administration and other back-office functions together in central units. All processes were to be streamlined and a restructuring of sales and marketing was expected to provide savings and free up resources for growth initiatives, while some jobs would be lost.

This was also the purpose behind the establishment of a Global Business Services Centre in Krakow, Poland in 2014, which would operate as an offshoot of the *Simplify* programme and lead to the removal of 120-130 jobs in Denmark over a number of years, mainly within IT and finance. The department in Krakow now handles functions in a number of areas, not just IT and finance, and has around 100 employees.

In all, the *Simplify* initiatives were expected to produce annual net savings of DKK 100 million from 2016.

Innovate presaged a continued high rate of innovation with significant investments in research – at the time over 20 per cent of revenue – to help redefine the treatment of allergy and asthma by making allergy vaccination widely available. The key element were the vaccine tablets, which would cover the major global allergies – grass, house dust mites, ragweed and tree pollen – by 2016, while the company also planned to extend the tablets' indications to new areas such as asthma.

Grow involved initiatives to maintain ALK's continued growth in Europe, although the underlying allergy vaccine market was stagnating. In other words, the aim was to gain market share, focusing especially on the two biggest markets, Germany and France. The latter was the home market for ALK's competitor, Stallergenes, but ALK had great hopes for an agreement to sell GRAZAX through the French sales force of Merck (known as MSD outside North America), majoring on respiratory conditions and extensive contact with doctors and patients.

In North America and Japan, ALK based its efforts on the agreements with Merck and Torii, and US launches of the allergy vaccines for grass and ragweed allergies were crucial to the fulfilment of the strategic plan. Along with milestone payments, ALK would start to receive royalties from sales, and income from the production of tablets for the American market. A tablet for house dust mite allergy was expected to launch in the USA in 2016, when the *Simplify* initiatives would also take full effect.

The company also intended to expand its global presence by entering a number of new growth economies where there was a sharp rise in the prevalence of allergies, and the business in China was to be developed.

New tablet vaccines on the way

Instead of progress however, 2013 was another year of reversals – this time more substantial as revenue declined by DKK 101 million to DKK 2,244 million. The number of employees also fell for the first time since the launch of GRAZAX, albeit with a modest loss of 24 full-time equivalents, leaving 1,804 employees.

The decline was mainly due to a fall of DKK 128 million in the milestone payments from Merck and Torii. Another factor was a setback for the JEXT adrenaline pen, which was withdrawn at the start of November when ALK's regular inspection process found a potential fault in batches produced in mid-2013.

The error rate was estimated at 0.04 per cent, which was enough for the company to withdraw the product at a time when it had sold 186,000 pens and taken 20 per cent of the European market: 'This is something that should not happen,' said then Director of Communications, Martin Barlebo, 'but it is also something that does happen.' Around 112 pens were adjudged to have the possible fault, but all products were recalled just the same and patients were supplied with a rival product. JEXT only gradually came back onto the market in 2014.[89]

In March 2013, on the other hand, Merck was able to submit an application to the FDA to register the grass allergy tablet, which went by the name GRASTEK in North America. This was followed just two months later by the application for the ragweed allergy tablet called RAGWITEK. At the end of 2013, the FDA's expert panel for allergy preparations unanimously recommended that GRASTEK should be approved, and a unanimous endorsement of RAGWITEK – the equivalent product for ragweed allergy – followed in January 2014. Only the final approval from the FDA was then needed before the two preparations could be launched.

Although it had every reason to expect FDA approval and launches of GRASTEK and RAGWITEK in 2014, ALK nonetheless decided to suspend its financial targets for 2015. It was still well short of revenues of DKK 3 billion – and even further from operating profits of 25 per cent. The decision was attributed to market conditions in Europe which were tougher than expected, and uncertainty around the launch and pricing of the tablet-based vaccines in the USA.

Things went to plan in the USA, as Merck obtained FDA approval for GRASTEK and RAGWITEK in April 2014 and placed both preparations on the market the month after – which was however too late for the pollen season, so they did not achieve big sales. Stallergenes had gained approval for its own grass allergy tablet two weeks before, but ALK did not feel threatened as the label for GRASTEK was 'much stronger' than Stallergenes' product, according to Jens Bager. GRASTEK was approved for children down to five years old, while Stallergenes could only be used from ten years upwards – and around 40 per cent of prescriptions were issued for children. Stallergenes' preparation also complicated the treatment of ten- to seventeen-year-olds, as they had to take increasing doses, which was not the case with GRASTEK.[90]

Also in April 2014, Merck initiated the final clinical trials in the USA on the tablet vaccine for house dust mite allergy. Further advanced with the same vaccine was Torii, which published the results from its final clinical trials two months later and announced that it expected to send a application for registration within months. Furthest ahead in development was ALK, which submitted a single European registration application for the tablet vaccine in November 2014 – seeking an indication not only for house dust mite allergy, but also for allergic asthma.

With concurrent trials in Europe, the USA and Japan, the work on the tablet vaccine was the largest-ever development programme in the field of allergy vaccines and was now entering its final phase.

With concurrent trials in Europe, the USA and Japan, the work on the tablet vaccine was the largest-ever development programme in the field of allergy vaccines.

In parallel with this, Torii launched a Phase II/III trial of the tablet vaccine for cedar wood allergy in September 2014, taking it into the late development phase. ALK was also continuing the development of a tablet vaccine for tree pollen allergy and expected to complete a Phase III trial before the end of 2016. All in all, then, ALK was well on the way to its target of a portfolio of tablet vaccines against four of the most common allergies caused by grass, ragweed, house dust mites and tree pollen, along with the development of the tablet for cedar wood allergy.

The immediate focus was on the tablet vaccine for house dust mite allergy, which had huge sales potential as house dust mite allergy is the most common allergy in the world and is not seasonal. The breakthrough came in August 2015, when ALK gained EU approval for the preparation to treat adults for both allergic hay fever and allergic asthma.

The latter was described by Henrik Jacobi as 'revolutionary' as it made the house dust mite allergy tablet the first modern immunotherapeutic medicine with a documented effect on asthma, which could open up a big new market, especially if the large-scale GAP trial on children also lived up to expectations.[91] The tablet was launched in Germany and Denmark at the beginning of January 2016 under the product name of ACARIZAX.

However, ALK's partner for Japan, Torii, got there first, launching its house dust mite tablet in December 2015 after it was approved for the treatment of adults with allergic hay fever – but without an indication for asthma. The Japanese brand name was MITICURE, and in preparation for the launch, Torii had previously launched two other ALK products, the SOLUPRICK skin test to diagnose house dust mite allergy and an injection-based vaccine to treat it.

ACARIZAX blister card.

In the USA, the prospects of launching the house dust mite tablet were slightly further off, although Merck did publish the results from the final Phase III trial in June 2015, which showed a significant improvement in the primary endpoints for the effect of the tablet vaccine. However, the results and the next steps had to be discussed with the FDA before a registration application was submitted in February 2016.

On the other hand, Torii submitted an application to register the tablet vaccine to treat cedar wood allergy at the end of 2015, while looking at a longer time frame for ALK's tablet for tree pollen allergy.

The FDA's approval of GRASTEK and RAGWITEK and Merck's launch of the clinical Phase III trial of the house dust mite tablet triggered three milestone payments to ALK totalling DKK 178 million, which were a big reason why total revenue in 2014 grew by 9 per cent to a record DKK 2,433 million.

In 2015 and 2016, the milestone payments from Merck and Torii were expected to run to DKK 170 million, after which they would stop. Conversely, royalties from sales of GRASTEK and RAGWITEK in the USA were starting to come in from 2015 and would be followed by royalties from both Merck and Torii for sales of the house dust mite tablet.

From one vaccine tablet to a complete portfolio

The launch of GRASTEK and RAGWITEK in the USA in May 2014 brought in the first new tablet vaccines from ALK since the introduction of GRAZAX in 2006 – albeit only RAGWITEK was to treat a new allergy. This was followed at the end of 2015 by the approval and launch of ACARIZAX/MITICURE against house dust mite allergy in the first EU countries and Japan.

After almost ten years, the company was finally able to offer a portfolio of standardised and registered tablet-based vaccines for grass, ragweed and house dust mite allergy – with further tablet vaccines for tree pollen and Japanese cedar wood allergy on the way. In marketing terms, this was a big advantage, as the tablets were now able to treat a range of allergies rather than being an isolated solution for a single allergy in a portfolio that otherwise consisted of injection and drop-based vaccines.

Another advantage was that many patients suffered from multiple allergies, and where they could previously be treated with GRAZAX for grass pollen but still had to have injections against the other allergies, most cases could now be treated with tablets alone. ALK was also alone in marketing a tablet vaccine approved for the treatment of both allergies and asthma caused by house dust mites.

At the same time, there was a big disappointment when the results from the five-year GAP study were published in January 2016 and showed that the study had failed on its primary endpoint, which was to document that treatment with GRAZAX could reduce the risk or delay the development of asthma in children and young people.

GAP was a pioneering study and a positive outcome could have had a huge impact on ALK, as GRAZAX would then have been the first and only medicine capable of preventing asthma. The timing would also have been ideal in terms of positioning ALK's overall tablet portfolio and, all in all, GAP could have been a game-changer in driving the final breakthrough for ALK and its tablet-based vaccines.[92]

That didn't happen, but there was strong evidence for the secondary endpoints, showing that GRAZAX significantly reduced

Søren Niegel, Executive Vice President, Commercial Operations since 2018.

the proportion of children with allergic hay fever who experienced asthma symptoms or took asthma medicines, and that the effect persisted for two years after treatment stopped. As such, the study did demonstrate a preventative effect on asthma, and the view within ALK today is that the primary endpoints set at the request of the regulatory authorities were too tightly worded and impossible to achieve: 'I do not think these endpoints would have been demanded by the authorities today,' said Søren Niegel.[93]

New partnership agreements

While expanding and strengthening the company's tablet portfolio, ALK was also extending its geographical presence by way of several new partnership agreements, as the company itself did not yet have the necessary financial and organisational resources to expand organically. In 2014, Abbott Laboratories in the USA was granted exclusive rights to register and market ALK's vaccine tablets in Russia and a number of neighbouring countries where ALK had not previously had a presence. The first registration process to be initiated was for GRAZAX, in expectation of a launch in 2017.

The partnership was extended in January 2016 to cover southeast Asia, with Abbott picking up exclusive rights to register and market the house dust mite allergy tablet in Hong Kong, Malaysia, the Philippines, South Korea, Taiwan and Thailand – and area with a total of more than 350 million inhabitants, and where house dust mite allergy was the most prevalent allergy. The first launches were expected in 2017. The agreement with Abbott was particularly advantageous as ALK had the option of taking back the rights once Abbott had cultivated the new markets.

Also in 2014, ALK entered into a partnership agreement in April with the China-based pharmaceutical company, Eddingpharm, for sales and distribution of ALK's products in China. ALK already had a sales office in China which had been posting double-digit growth rates for a number of years, but the market remained very modest even though around 200 million Chinese people suffered from allergies, including 100 million with house dust mite allergy.

In the first instance, the agreement covered the SOLUPRICK and ALUTARD products (to diagnose and treat house dust mite allergy, respectively), and ALK also started up a local development programme for the house dust mite allergy tablet with the long-term aim of registering and launching it in China. The agreement ran for nine years and trebled ALK's sales force when combined with the Chinese company's sales activities in the treatment of lung conditions.

In February 2015 it was the turn of Australia and New Zealand, where ALK entered into a partnership agreement with the Australian pharmaceutical company, CSL Seqirus, which was granted exclusive rights to register and market ALK's tablet vaccines for house dust mite and grass allergy, and the JEXT adrenaline pen, in these two countries. Allergy was the fastest-growing chronic illness in Australia, with around 20 per cent of the population suffering from at least one allergy.

SOLUPRICK SQ used for allergy diagnostics (skin prick test).

ALUTARD injection vaccines.

When the agreement was signed, the leading medical companies and patient organisations for allergy in Australia were developing a national allergy strategy, whereby allergic diseases would be recognised as a national health priority area. So the long-term growth prospects for ALK's tablet vaccines were promising.

In parallel with the partnership agreements, ALK was also building up its own presence in new markets, establishing a subsidiary in Slovakia in 2014 to enable the company to grow faster in eastern Europe, and in Turkey, where it also set up a subsidiary. The following year, ALK bought out its Turkish distribution company and integrated it into the subsidiary.

Allergy unlocked

Finally in 2014, ALK launched an initiative to expand the market in Europe. *Allergy unlocked*, as the initiative was called, was an umbrella term for a range of activities intended to improve access for allergy sufferers to immunotherapy and to make it easier for them to receive treatment.[94]

As the Chairman of the Board of the Lundbeck Foundation, Arne Jensen, had said years before, the success of the tablet-based vaccines was dependent on the company's ability to create a market. However, this also required the tablets themselves to force a change in the existing market with its competing injection-based products, which were cheaper but had no documented effect and lacked regulatory approval.

The fact was that the vaccine tablets simply did not fit into the whole institutional infrastructure surrounding the allergy vaccine market, with its registration and reimbursement schemes and existing procedures and incomplete guidelines.

With GRAZAX as its only tablet-based vaccine, it was too large a task for ALK to make a serious impression on this system. However, the creation of a wide portfolio of tablets brought fresh possibilities, and on this basis *Allergy unlocked* was launched with the aim of altering the allergy vaccine market through systematic work with patients, doctors and authorities, to bring the use of evidence-based and approved products into the foreground and to raise the level of treatment.

The activities covered five areas, focusing on documentation and information on the personal, social and economic consequences of uncontrolled allergy, and how evidence-based treatment with allergy immunotherapy could have a positive effect on patients and on society at large.

A major factor was getting medical experts, whether individuals or associations, to advocate the use of evidence-based vaccines, so the company also wanted to work with national and international associations of allergologists to get allergy and allergy treatment on the public and health policy agenda.[95]

Success at a competitor's expense

The years 2014-2016 looked to be a turning point for ALK, with the establishment of a diversified tablet portfolio and geographical expansion through new partnership agreements. The financial results for 2015 pointed the same way, with revenue growing by almost 6 per cent to DKK 2.57 billion and operating profit (EBITDA) reaching DKK 452 million.

These excellent figures exceeded the original expectations of the company and financial analysts and were due mainly to very strong growth in the fourth quarter. The reason was that, at the beginning of December 2015, the company's strongest competitor, Stallergenes, was ordered by the French health authorities to suspend production and withdraw all of its products from the middle of August, after problems with a new IT system had resulted in incorrect deliveries to a number of patients.

Stallergenes had merged with the US allergy vaccine firm, Greer Laboratories, in September 2015, to create a company with revenue and global market share on a par with ALK's. Both Stallergenes and Greer were controlled by the UK-based Ares Allergy Holdings plc, which now challenged ALK's position as the world's largest allergy vaccine manufacturer but was hit hard by the French injunction.

Per Plotnikof, Vice President, Corporate Communications, Investor Relations and Strategic Planning since 2015.

The analysts were quick to see the situation as good news for ALK, which had an unexpected opportunity to gain market share in France, where Stallergenes-Greer was the clear leader, and in other European markets: 'One man's loss is another man's gain,' in the words of an analyst from Sydbank. The view within ALK was more cautious: 'This is a very serious situation which affects many thousands of patients', said ALK's Head of Communications and Investor Relations, Per Plotnikof, adding that the company intended to discuss things with the French health authorities and make its resources and products available: 'We will do all we can to help the patients, and when the implications are known, we will have to assess how this will affect our business.'[96]

It was just at the start of the peak treatment period ahead of the pollen season, so Stallergenes-Greer was hard-hit as its patients were forced to look to treatments from other manufacturers – mainly ALK.

So ALK stepped up its production and took on 80 new employees at its factory in France, but it was still hard-pressed to cope with the sudden growth in demand.

One disappointment in the otherwise good annual results was the unexpectedly modest sales of tablet-based vaccines in the USA, which had already drawn criticism when the half-yearly figures were published: 'A fly in the ointment,' was one financial analyst's view of US tablet sales, which brought in just DKK 44 million.[97]

ALK's Chief Executive, Jens Bager, was not happy either: 'I have to say that things have gone a lot slower than I hoped and expected,' he said, adding that the disappointment also had to be viewed 'in the light of Merck's expectations.' However, he also acknowledged that the disappointing tablet sales were not just an American problem, but that neither ALK or Torii had achieved the expected financial results from the scientific breakthrough and the new tablet products: 'What we are failing to show, and our partners in Japan and the USA are also failing to show, is that we can make a commercial success of this,' was his verdict on the companies' performances.[98]

This view was confirmed by the annual report, where tablet income from Merck and Torii contributed DKK 312 million, or just 12.1 percent of ALK's total revenue – nine years after the launch of GRAZAX.

At a crossroads with new management

Success for ALK looked likely to continue when Stallergenes-Greer announced in January 2016 that production in France would be suspended at least until March, which meant that ALK could count on a more prolonged increase in demand. In any event, many of Stallergenes' patients who had started treatment with ALK's products were expected to continue even after Stallergenes resumed deliveries, as it was no simple matter to just switch between the two companies' preparations.

A feather in ALK's hat in the French market came when the health authorities approved ACARIZAX and issued a marketing authorisation at the end of January 2016. However, an agreement on pricing and reimbursement was required before the preparation could be placed on the market, and ALK banked on this happening quickly.

ALK's annual report for 2015 was therefore acknowledged not only for its good results but, as analysts noted, 'a good set of expectations' for 2016, as one from Jyske Bank put it – a view that was widely shared.[99]

The company's expectations were also well above what the analysts and the market had expected. Excluding milestone payments and royalties, the company expected organic growth of 10 per cent in the core business, and growth of no less than 35 per cent in operating profit. On top of this came potential milestone payments of DKK 75 million and royalties from the partner companies in the USA, Japan and Australia.

Just a week later, in the middle of February 2016, came the positive and long-awaited news from the USA that Merck had submitted an application to register the house dust mite tablet, which was expected to give a significant lift to ALK's North American tablet business.

There was every sign, therefore, that 2016 would be a particularly successful year for ALK, so it also came as a big surprise when the company announced on 22 February that its Chief Executive, Jens Bager, was stepping down with immediate effect: 'The Board believes that this is a good time to look for new chief executive,' said the Chairman Steen Riisgaard, emphasising that the company was in an exceptionally favourable position and that was the perfect time to seek a new chief executive.[100]

Steen Riisgaard praised and thanked Jens Bager for his efforts at the head of ALK for 16 years and stressed his importance to the development of ALK's platform with a complete portfolio of vaccine tablets to treat hay fever and asthma. This gave the company a strong foundation for growth, 'but we are at a crossroads, as we enter a new phase focusing on the commercialisation of our evidence-based products,' Riisgaard explained. So there was a need for 'someone who can market and commercialise the platform and take the company to the next level.'

However, ALK had no replacement in mind: 'We are casting the net very wide – at home and abroad. We need someone with the right commercial skills,' said Steen Riisgaard, and until this was in place, he would continue as Chairman with extended responsibilities, and so act as the company's general manager.[101]

Among the analysts, the news was received with a certain puzzlement because of the timing and because the company did not have a replacement ready. A senior analyst at Sydbank noted, for example, that the company had no CEO at a time when it was 'working flat out' to take advantage of Stallergenes' suspension of production: 'Now is the time to make the most of Stallergenes' problems, so the change of CEO could throw a spanner in the works.'[102]

An analyst from the finance house Sundal Collier agreed: 'Now you find yourselves in one of the most important periods in the company's history, the next twelve months, and you will probably be without a chief executive to take the final decisions,' he said. It would take four-to-six months to find a new CEO and perhaps a few months more before that person could start.[103]

And it was a good ten months before a replacement for Jens Bager was able to start work. When ALK announced in mid-May 2016 that it had hired Carsten Hellmann as its new CEO, it was with an expected start date of 1 January 2017. Carsten Hellmann had been CEO of Sanofi's veterinary business, Merial, since 2013, and also Executive Vice President and member of the Group Board of Directors of Sanofi.

After effecting a turnaround at Merial, Hellmann was in the process of selling the company to Boehringer-Ingelheim – and would only join ALK after that.

7.

New management and growth strategy

‘Making our own way in the USA’

In July 2016, about two months after Carsten Hellmann was named as the forthcoming Chief Executive of ALK, the company received the unexpected and depressing news from Merck that it intended to discontinue the partnership to develop and market ALK’s vaccine tablets in North America. All rights to GRASTEK, RAGWITEK and the house dust mite tablet would pass to ALK free of charge after six months and the registration process for the last of these would continue, to be gradually taken over by ALK.

Merck referred to a strategic decision to re-prioritise its resources, and the US company was also facing a gaping hole in earnings with the imminent expiry of patents on two cholesterol preparations with annual sales running to USD 3.6 billion. Sales of ALK’s allergy vaccine tablets had also produced a very modest income of around USD 14 million in 2015, well below the marketing costs, and ALK was also entitled to 15 per cent in royalties. Merck therefore chose to focus its resources on other areas.[104]

Carsten Hellmann, CEO at ALK since 2017.

The news from Merck pulled the rug out from under ALK’s North American tablet strategy, and the Danish Stock Exchange reacted with an immediate 18 per cent dive in ALK’s share price, although analysts still had faith in the potential of the vaccine tablets across the Atlantic. So did ALK, and the Lundbeck Foundation also remained optimistic: ‘Of course this raises some challenges in the short term,’ said the Chief Executive of the Foundation, Lene Skole, ‘but ALK now has the chance to rethink its strategy for the USA, and we think that could turn out very well in the longer term.’[105]

With the transfer of the North American rights to the tablet vaccines, ALK would benefit from the fact that the substantial development and registration costs for the vaccines had already been financed by Merck.

On the other hand, an issue for the company was that the American allergologists who were to prescribe the tablet vaccines had a lucrative business from treating their patients with regular injections of allergy vaccines they mixed themselves from allergens supplied by ALK and others. If the patients were prescribed tablets which allowed them to manage their own treatments, the allergologists would lose a good deal of income, and this was the crucial structural barrier to the adoption of tablet-based vaccines in the USA.

Despite its size and strong position in the US pharmaceutical market, Merck had not managed to overcome this hurdle. The question then for ALK was whether to find a new partner or try to distribute its tablet vaccines for itself – or whether to try a combination of the two?

For the moment, the management and Board of Directors decided to await the arrival of Carsten Hellmann as CEO before plotting a new strategy. However, the company did start to build up an American sales organisation, taking on 50 new employees to add to those selling allergens and diagnostic equipment. ‘We will be ready when it is time to take over the baton from Merck, ’ promised the Chairman, Steen Riisgaard.[106]

The company further strengthened its presence in the USA at the end of 2016 when it acquired two American companies, Allergy Laboratories and Crystal Laboratory, for DKK 138 million; these produced

allergen extracts and other materials for treating allergies, including vials and diluents which were useful to the American allergen business.

So ALK had to strike a difficult balance, supplying allergens to American allergologists and aiming to expand this business while also trying to get them to prescribe tablets.

Tighter quality requirements and greater regulatory control

While American sales of tablet-based vaccines were disappointing, there was progress in the European business where ACARIZAX became the biggest-selling allergy vaccine in Denmark and Germany to new patients with house dust mite allergy in the space of just six months. Overall, the company was making big advances, largely due to Stallergenes-Greer's difficulties, although the French company was cleared to resume full production in March 2016.

Most of the patients who had switched from Stallergenes-Greer's preparations to ALK's had continued to use the Danish drop and tablet vaccines, and to keep up with the demand, the capacity at the company's factory in France was boosted with 50 new employees.

On the other hand, there was a fall in sales of injection-based vaccines, due mainly to the phasing-out of Avanz where ALK did not yet have a replacement to offer, while an upgrade to the company's quality assurance system affected the production of injection vaccines, which had the oldest manufacturing facilities.

The upgrade was meant to ensure that the company's production facilities would comply with the health authorities' quality and safety requirements for the production of medicines, which were getting tighter all the time – as were the regulatory controls. In the first ten months of 2016, for example, ALK had eleven control visits – including one by the US FDA, which carried out a twelve-day inspection at Hørsholm in March, focusing especially on the production of Pharmalgen to treat bee and wasp allergy.[107]

ALK's production site in Varennes, France.

The inspection resulted in an *Untitled Letter*, which cited a number of deviations from Good Manufacturing Practice (GMP) but, unlike a *Warning Letter*, did not contain any sanctions or threats of sanctions. The FDA could not shut down production in Hørsholm but could threaten a ban on exports to the USA, for example, if certain requirements were not met.[108]

It did not come to this, but it was still a serious letter, just one level below a *Warning Letter*. The FDA not only raised a number of issues with the production of Pharmalgen, but also noted that ALK had no

fixed written procedures and routines to prevent microbiological contamination, either in the overall manufacturing process or in the subsequent checks on the finished products.[109]

The control visit prompted ALK to step up its efforts to comply with the FDA's requirements, which reduced production capacity and caused sales of injection vaccines to slow in the second half of the year. Nevertheless, 2016 was a record year for the European business, which grew by a full 28 per cent to almost DKK 2.5 billion.

There was good progress in North America too, despite the slow take-up of RAGWITEK and GRASTEK. Sales of allergens and diagnostics and other allergy products increased by 12 per cent to DKK 449 million and, with a milestone payment and royalties from Merck of DKK 63 million, this brought growth in the USA up to 15 per cent.

Sales were generally strong in all markets except Germany, which was hit by the reduced production capacity for injection vaccines, and there was a decline in China which led ALK to drop the partnership with Eddingpharm.

The total revenue in 2016 came to almost DKK 3 billion, while the operating profit (EBITDA) increased by 35 per cent to DKK 705 million, with a profit margin of a full 23 per cent – close to the earlier financial target of 25 per cent.

This success could also be seen in an increased headcount, which grew by over 150 to a total of 2,010 employees.

'We need to take control'

So, when Carsten Hellmann joined as Chief Executive in January 2017, ALK was doing well, with Stallergenes-Greer's difficulties the main reason for the exceptionally strong growth. A key task in the new year was therefore to sustain this progress, and the company set out to retain a market share of more than 50 per cent and, with that, its newly-acquired position as the largest allergy immunotherapy company in France.

The overwhelming priority, however, was the challenge it faced in America after Merck discontinued the partnership, and this was also a key topic when Carsten Hellmann was asked about his plans in an interview shortly after coming on board: 'We need to take control,' he said of his intended approach to tackling the issues in the USA. He flatly refused to 'chase the rainbow' as he put it – to look for a partner to handle everything and bring in the billions. He did not rule out one or more future partnerships around specific preparations or areas, but 'to begin with, we are on our own in America, and then we'll see what happens.'[110]

The crucial thing was to tackle the lack of any incentive for the allergologists to prescribe tablet treatments, and Carsten Hellmann did not harbour any hopes that ALK's salespeople would do better than Merck's in persuading them to switch to the tablets. Rather, it was important to understand what he called the 'ecosystem' around the allergologists, and to involve the patients and patient associations and develop apps and digital systems to be shared with the allergologists and help them to develop their business.

In the present situation, many American patients chose not to receive treatment, so the task for ALK was to do all it could to help the doctors reach the patients who were leaving the clinic empty-handed, bringing growth to the doctors' businesses with the tablet treatment supplementing their existing revenue.

Carsten Hellmann also announced changes within ALK, which he said was transforming itself from a niche operator supplying allergens to the allergologists to a dedicated pharmaceutical firm developing and registering its own medicines. This called for changes in the

Carsten Hellmann also announced changes within ALK, which he said was transforming itself from a niche operator supplying allergens to the allergologists to a dedicated pharmaceutical firm developing and registering its own medicines.

organisation and in the employees' mentality and attitudes, to enable the company to react quickly and flexibly to changes and seize new opportunities.

For the management, this meant deciding where the potential lay and presenting an action plan where there should be little difference between the goals the company wanted to achieve and how the employees saw themselves: 'We need to have a coherent set of ambitions so people can see that they have a realistic chance of succeeding,' he explained.

Hellmann pointed out that this was how he had effected a turnaround at Merial – without changing the employees. So he had no intention of making large-scale changes in the workforce; it was a matter of unleashing people's potential. All in all, he felt that ALK had 'huge untapped potential ... which no-one has really cracked the code for so far, and that is my ambition,' he declared. 'But it is a pragmatic ambition. Not a dream scenario.'[111]

The key message was that ALK needed to create an organisation 'that can take charge out in the countries.' ALK could not maintain a presence through partners alone, but this did not mean that it should not collaborate with others. However, large pharmaceutical companies could quickly change their focus and strategy, as had been seen with Merck, 'so we cannot wait for others to succeed for us', was the message from Carsten Hellmann: 'The answer is to take our destiny into our own hands and get this organisation to pull together so we can do that.'[112]

'The most important approval in ALK's history'

However, it was a while before ALK was able to take control of the tablets business in the USA. The reason for this was that the American approvals for GRASTEK and RAGWITEK had been issued to Merck, and any transfer of the product licences to ALK would have to be approved by the FDA.

The same procedure would apply to the tablet vaccine for house dust mite allergy, which was approved by the FDA at the beginning of March 2017. But the approval, and hence the marketing authorisation, belonged to Merck, which had submitted the application. Authorisation from the FDA was required for Merck to transfer the approval to ALK, and a similar procedure applied in Canada, where the preparation had been approved in May.

Nevertheless, there was great delight in ALK, where Carsten Hellmann described the approval as 'the start of a new era for ALK in the USA,' while Research and Development Director Henrik Jacobi called it 'the most important approval in ALK's history.'[113]

According to Jacobi, the tablet-based vaccine was 'potentially the biggest product in definitely the biggest market'. It was estimated that 30 million Americans suffered from house dust mite allergy, and around a tenth of them were candidates for allergy immunotherapy. The finance house Jefferies suggested that the approval could bring revenues of USD 200 million to ALK.

In the longer term the market could be even bigger.

The approval covered the treatment of adults aged eighteen to sixty-five, but ALK intended to run fresh clinical trials with a view to getting the tablets approved for children and adolescents, and to discuss with the FDA what it would take for it to be approved for the treatment of asthma, as it was in Europe. According to Jacobi, however, there was a realistic time frame of several years before the two approvals could be obtained, 'but that should not spoil our pleasure at this approval.'[114]

While ALK waited for the FDA to approve the transfer of the product licences from Merck, the company continued to upgrade its American organisation. The very day after the tablet-based vaccine for house dust mite allergy was approved, the company announced that it had hired a Dane, Hendrik Nolte (MD, PhD) to head up the clinical development activities in the USA and some international markets outside Europe.

Hendrik Nolte, who had been employed by Schering Plough in 2005, later became part of Merck, where he led the development and registration efforts for ALK's grass, ragweed and house dust mite tablets, so ALK gained a person with many years of experience in the development of allergy and asthma drugs for the American pharmaceutical market.[115]

The ambition to be able to use the house dust mite tablet to treat asthma in the USA and other countries outside Europe received a boost at the end of February 2017 when independent international experts from the Global Initiative for Asthma (GINA) recommended the use of tablet vaccines to treat adult patients with moderate allergic asthma.

GINA was (and is) a global network of asthma experts which was established in 1993 in collaboration between the World Health Organization (WHO) and departments of the US Department of Health and Human Services. The recommendation was given in an updated guideline to healthcare professionals and policy-makers, and although GINA did not mention one or more specific preparations, ACARIZAX was the only tablet-based vaccine for house dust mite allergy which also carried an asthma indication. The recommendation also referred to clinical trials of ACARIZAX, and there was great enthusiasm within ALK too: 'This is huge for us,' said Henrik Jacobi.[116]

However, the approval in the USA covered the indication for allergy and not for asthma, but Henrik Jacobi still believed that the recommendation from GINA could have a major bearing on the launch and take-up of ACARIZAX. Although the preparation could not be launched in the USA as a treatment for asthma, the recommendation would serve as a lever to induce the allergologists to prescribe the tablet for patients with both allergic hay fever and allergic asthma.[117]

The efforts to extend the patient group to include children and adolescents were also progressing, as ACARIZAX had its European approval extended in mid-April 2017 to cover young patients aged twelve to seventeen. After a series of clinical trials, the company's Japanese partner, Torii, had also submitted an application to extend the patient group for MITICURE to include children all the way down to five years old. The preparation was already approved for allergy patients aged twelve to sixty-four.

Two bits of good news – and one bad

On 21 August 2017, ALK was finally able to announce that the FDA had approved the transfer of the American product licences from Merck to ALK: 'It was so nearly there the whole time,' said Carsten Hellmann of the long drawn-out process, where it seemed again and again that the decision was just around the corner. On the other hand, the company was well prepared after spending six months building up the core organisation in the USA, and Carsten Hellmann affirmed that ALK was ready to invest a further DKK 75 million to bring forward the launch of the house dust mite tablet in the USA (ODACTRA) and Canada (ACARIZAX) and get off to a good start.[118]

A month later, ALK made another encouraging announcement when the final Phase III trials of the tablet-based vaccine, ITULAZAX, showed the most convincing results yet: 'These are fantastic figures,' said Henrik Jacobi, adding 'that there should be no doubt that the authorities will approve this product.' The company would therefore be submitting applications for European and possibly Canadian registration in 2018.[119]

This trial was the first in which ALK used a new model for allocating patients, developed after a clinical trial had failed because of a poor pollen season. Here, the company collected the last ten years' pollen counts from the whole of Europe and used a computer simulation to develop a model to obtain usable results for all ten years by splitting the patients into different geographical areas so low pollen counts in some areas were offset by high counts in others.[120]

Just a week later, however, came bad news from ALK, which announced on 21 September 2017 that the French health authorities were demanding an update to the quality assurance systems in the company's French factory at Vandeuil, with an order to shut down a small production line in the same factory.

The reason for the order was contamination of the environment in a sterile area where injection-based vaccines and skin prick tests were manufactured, but the production of drop-based vaccines was not affected. In fact the shut-down was extremely limited, covering just 0.5 per cent of ALK's total annual revenue, and the company was quick to emphasise that the shut-down was in no way comparable to the closure of Stallergenes' French factory at the beginning of 2016.[121]

Nevertheless, the shutdown was 'a bit of a blow for us', recalls Christian Houghton, who was then Vice President in charge of pharmaceutical product development.[122] The worry was that the order could place further restrictions on what could be produced and distributed, but it did not go beyond the limited shut-down as ALK pushed the ongoing work of upgrading and quality-assuring the company's production facilities not only in France but across the board.

The French shut-down came about a year after the criticism levelled by the FDA at the production facilities in Hørsholm, and the timing was critical as ALK was busy drawing up a new growth strategy which was to define the way forward for the company. The growth strategy was also to be financed by a capital increase in the form of a share issue, and now 'the cannonballs were rolling around the deck while ALK struck out for fresh horizons,' as Carsten Hellmann put it.

Christian Houghton, Executive Vice President, Product Supply since 2019.

The French shut-down was not rescinded until the summer of 2019, after ALK had demonstrated that the conditions at the facility complied with the authorities' requirements. By that time, the growth strategy had long been adopted and was well on the way to being implemented.

Three-year growth strategy

On 4 December 2017, ALK published its new growth strategy, which was to run for three years and build on the company's leading position within allergy vaccination and provide for a broader global presence within allergy and allergic asthma. The strategy consisted of four key areas, which were mutually dependent and were therefore to be addressed in a single integrated process:[123]

1. Conquest of the American market, where the company planned to invest around DKK 1 billion in a number of initiatives over three years, with ODACTRA cast as the 'battering ram' to break down the defences. This preparation was independent of the pollen season and could be prescribed all year round; in Europe it was found to have a 'halo effect' in increasing sales of the other vaccines; and finally, it would open up the market in the southern states of the USA where grass and ragweed allergy were not so widespread.

As a means of establishing an American tablet market, the company proposed to run support and voucher programmes in the launch phase and enter into an agreement with an agency to help patients obtain assistance from insurance schemes. The company also planned to target activities at specific groups of patients and doctors as well as major opinion-formers in this area, and to persuade the allergologists that tablet vaccines would expand their business. It also planned to maintain the focus on supplying allergen extracts, as this area was expected to grow.

2. Complete the tablet portfolio with a view to getting all tablet vaccines, covering the five commonest respiratory allergies, approved for all relevant age groups. This would include a global clinical development programme aimed at extending the indication for ACARIZAX/ODACTRA to cover children and adolescents outside Europe too. Including the required supplementary monitoring studies of the three vaccine tablets on the American market, the total annual research and development costs over the next five years were expected to run to DKK 400-600 million.

3. Digital patient-facing activities and new business areas through the creation of a new Consumer Care division, which was to promote dialogue with patients via digital solutions and create a visible presence in the broad allergy marketplace and hence also for patients who were able to relieve their symptoms with antihistamines. ALK already had 2.5 million unique users on its web platforms, and these activities were to be extended to make direct contact with patients in the early stages of their illness in order to assist them with their allergy through guidance and advice and sales of other allergy products than vaccine tablets. The company also planned to seek out new and related business areas via partnerships or by licensing and acquiring products.

4. Optimise and prioritise ALK's resources to make production more efficient and improve long-term earnings, with continued rationalisation of the older product portfolio and transfer of allergy patients to the company's evidence-based and standardised preparations. The whole organisation was to be streamlined and upgraded to free up resources that could be reassigned to areas within the strategic growth initiatives.

ALK also launched a separate project as part of rationalising the older product portfolio, which was not just a matter of withdrawing products from the market but also of upgrading the products it decided to retain and continue to market.

The reason was that the tablets had not yet broken through completely and the legacy portfolio, as the older products were called, would remain a substantial part of the company's revenue base for many years to come.

At the same time the regulatory requirements for documentation and evidence were growing all the time, and the main purpose of the Product and Site Strategy (PASS), as the project was dubbed, was therefore to assure and document the quality of the products and the

evidence for them as a basis for keeping them in the company's portfolio. If this could not be done, the relevant products would be withdrawn from the market – even if it cost the company on the income side.

Although the strategic plan took in four key areas, it covered all sides of the company's operations. When the strategic plan was published, Carsten Hellmann stressed once more that the intention was more far-reaching than that; it was to effect a transformation of ALK to the point where the company would no longer be regarded as an allergy or immunotherapy tablet business but as an allergy company – and ultimately *the* allergy company.[124]

ALK's first share issue

The major investments entailed by the strategy would probably put a brake on earnings and produce negative cash flows of up to DKK 1 billion over the next three years. The company therefore announced that it was considering several financing options, including taking a loan or making a share issue, which would be a first for the company.

There was full support for the strategic plan from the principal shareholder, the Lundbeck Foundation, and a promise that, if there was a share issue, the Foundation would subscribe at least in proportion to its existing holding. However, the reaction from the equity markets was less enthusiastic, with the prospect of several years without any dividend payments, and the publication of the strategic plan triggered a 25 per cent fall in the share price.

Meanwhile, ALK was already well advanced in its efforts to obtain fresh capital, which came to fruition when it announced just three days after publication of the strategic plan that it had raised almost DKK 700 million from a 'book-building' issue which was over-subscribed by selected Danish and international institutional investors, who paid DKK 690 per share.

Carsten Hellmann in his office at ALK's headquarters in Hørsholm, north of Copenhagen.

Together with its existing credit facilities, ALK then had enough money to finance the big push in the USA and carry out the other initiatives: 'We know that we have full support for our strategic plan. Now we have financing for it through a share issue, and we will succeed with it,' said Carsten Hellmann.[125]

Ahead lay three crucial years for ALK.

8.

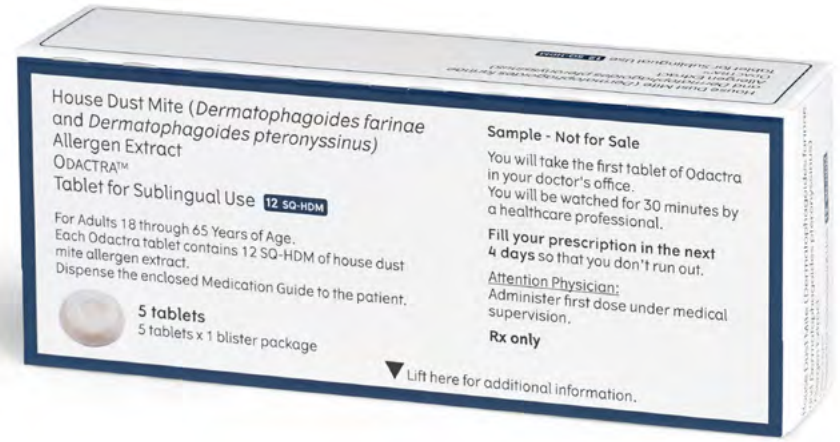
Turnaround

‘We are reaching our targets in the USA’

After months of preparation, ALK’s three-year growth strategy kicked off with the launch of the house dust mite allergy tablet ODACTRA in the USA in January 2018. The company did not reckon on immediate penetration of the market, setting a modest target for the first year of 5,000 new users, rising to 10,000 new users in 2020. By way of comparison, it had reached 20,000 new users in the first year in Germany, while France saw 2,500 new patients in the first five weeks after the preparation came onto the market. In Japan, Torii made a slow start before reaching around 2,200 new patients per month.

However, ALK emphasised that it would be a long hard road to break through with the tablet-based vaccines in the USA. The key to success was to convince the American allergologists that it would also be an advantage to them to start prescribing tablet-based vaccines alongside their normal injection treatments. ALK expected to succeed in this, and things appeared to be going to plan.

The house dust mite tablet ODACTRA, launched in the USA in January 2018.



At any rate, Carsten Hellmann declared at the beginning of May 2018 that ‘we will make it in the USA.’ About three months after the launch, 400 out of 2,000 selected allergologists had started to write prescriptions for ODACTRA, which was more than expected. The number of new patients was rising more slowly, with 1,300 starting treatment – but this was also more than expected.[126]

This progress was maintained, and Carsten Hellmann declared at the beginning of November 2018 that ‘the all-important news’ on the American market was that ALK now had confirmation that tablet-based vaccines had a future in the USA: ‘The fear that tablet sales in the USA would never take off is no longer there.’[127]

Around 1,100 allergologists were now prescribing ODACTRA, while the number of patients receiving treatment was some 3,500-4,000. American health insurers had also taken up ALK’s tablet vaccines, so 73 per cent of all those insured could claim reimbursement. The expectation was that, by the end of the year, 7,000 new patients would be receiving treatment, exceeding the target by 40 per cent.[128]

To give a further boost to this development, ALK launched an extensive digital campaign which was to run until February 2019 with the aim of ‘bringing patients in to the American doctors,’ as Carsten Hellmann explained: ‘We are pressing on all platforms, and bringing patients over to the doctors is our way of showing the allergologists that they can offer better treatment and pick up more business by working with us.’[129]

Lighthouse, cultural beliefs and spirit days

Another internal initiative kicked off in January 2018 when Carsten Hellmann and the senior management embarked on a tour of the company’s subsidiaries, branches and divisions around the world. The aim was to push the strategy process along by way of ‘town hall meetings’ for employees across departments and teams and to involve them in the work on the new strategy from the outset.

This process had already started within ALK at the start of December 2017 with the publication of the new strategy, when Carsten Hellmann introduced the strategy and goals on the company intranet, among other places. Gone were the usual *Key Performance Indicators* which allowed the company to measure its performance on selected key figures in order to assess how well – or badly – things were going.

Instead, the management had created a 'lighthouse' to symbolise the overall goal of the strategy, which was to turn ALK into the world's leading allergy company and not just the leading allergy immunotherapy company. ALK intended to be *the* allergy company where people with allergies would come for knowledge and information on possible relief and treatment, so they could be helped to a better life.

The idea of using a lighthouse was that it can be seen from a long way off, so you can navigate by it without knowing every step or turn along the way. It was easy to communicate this intention, so everyone could understand what the company was aiming at regardless of language, culture or function. It also signalled that all employees were to be actively involved in the process and help the company to reach its goals.

A successful transformation called for an internal culture change, with both individual employees and the business as a whole changing their self-perception and thinking of ALK as an allergy company and not just as an allergy vaccine producer.

A corporate culture had been established over decades where the emphasis was on research and development and producing the best allergy vaccines. On the other hand, there was less attention paid to getting the vaccines out to patients, and there was not the same focus on sales and marketing and on commercial activities throughout the organisation.

In this context, the role of the lighthouse was to point the way to the goal, which was to help patients to get treatment for their allergies. This was in a constantly-changing market landscape, so it was also necessary 'to ensure that everyone can see what is the right thing to do when we are guided by the lighthouse,' said ALK's then Human Resources Director, Pernille Tang Raschke. The company had therefore drawn up a new set of values comprising three new *cultural beliefs*, to support the cultural transformation of the business:[130]

- Do the right thing
- Pursue growth
- Build bridges

Each cultural belief was then broken down into a number of cultural behaviours, which were designed to inspire the employees in their work of developing and distributing new and improved treatments for allergy-sufferers all over the world.

The core of the three cultural beliefs was to give individuals greater responsibility and scope to take decisions and act in an agile way to create rapid and focused results; to see changes as fresh opportunities rather than limitations and obstacles; and to build bridges across functions and departments and produce shared results – a departure from the strong silo culture that existed previously within the ALK organisation.

With this introduction via the intranet, the work of bringing about this cultural change took off with the management 'world tour', with more than twenty 'town hall meetings' in fourteen different places around the world in January alone. The meetings were dubbed *spirit days*, and the aim was to bring employees together across departments and teams to discuss their work on the new growth strategy and the concept of the lighthouse and the new values. They involved groups of ten-to-twelve employees from different parts of the organisation, facilitated by around a hundred managers who had received training in how to drive change and act as role models.

However, the series of *spirit days* was just the beginning, and ALK was well aware that culture change is a lengthy process in which it is easy to fall back into old habits: 'The hard work starts now,' said the Human Resources Director Pernille Tang Raschke at the end of the run of *spirits days*, when all of the employees returned to their departments and their day-jobs and were urged to ask themselves: 'What do we need to differently here from Monday morning if we are to change and achieve our ambition of helping more allergy-sufferers?'[131]

ALK - the allergy company

The idea of using a lighthouse was that it can be seen from a long way off, so you can navigate by it without knowing every step or turn along the way.

Digital allergy platform and webshop

A key part of the new strategy was to expand the use of digital tools and adopt completely new ones in order to reach as many as possible of the 500 million people around the world who were estimated to suffer from respiratory allergies. Around 10 per cent ought to be receiving treatment with allergy immunotherapy, but only about 1 per cent, or 5 million people, actually were. ALK had a global market share of 35 per cent in this area.

Market surveys had also shown that there was a clear and increasing tendency for patients – and not only those with allergies – to treat themselves, and that around 60 per cent consulted their doctors only rarely. Instead, patients were increasingly using the internet as their primary source of information about their situation and possible treatments.

The intention behind the wider use of digital tools was therefore to pick up the 9 per cent of people around the world who suffered from allergies and ought to be treated with immunotherapy but were not. The aim was also to establish ALK in the broader allergy market for antihistamines and allergy-treated products, which was estimated to be worth more than DKK 120 billion altogether.

Before launching the three-year plan, the company had therefore run several pilot projects in 2017 in which ALK-run websites set out to motivate people with allergy to do something about their conditions. In Sweden, for example, patients were offered a skin prick test followed by a recommendation to consult an allergologist, while a project in Germany experimented with direct sales of allergy-related products.

Based on these findings, ALK's new Consumer Care division aimed to position the company in the broader allergy market as the leading authority on all forms of allergy and allergy treatment. The intention was that the company should not only offer immunotherapy to the hardest-hit but appeal to anyone with an allergy with the aim of being 'the preferred partner for allergy-sufferers, ' as the Director of the Consumer Care division, Mads Lacoppidan, put it when explaining the purpose of the new division in *Medwatch*.

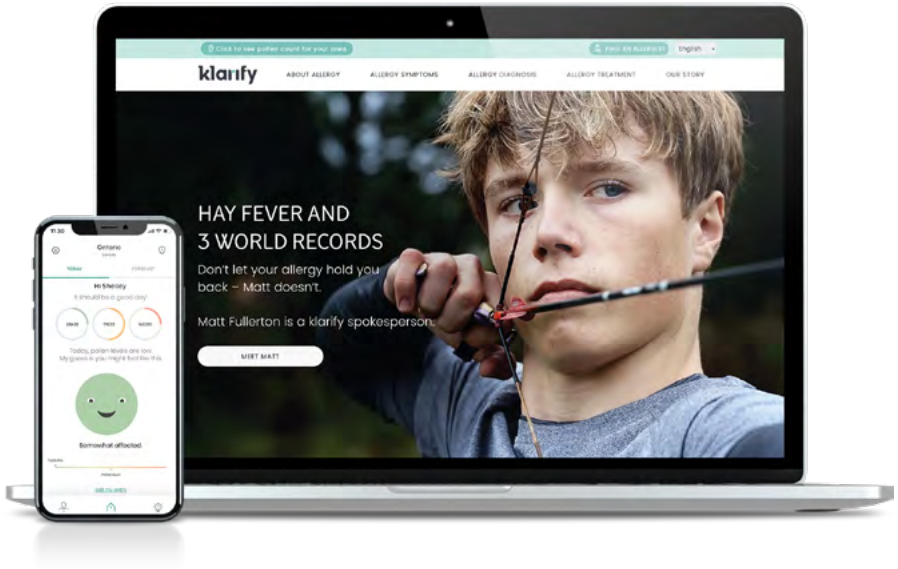
To this end, a new digital platform was to be set up where patients could go for information and advice. A radical new feature was that the platform would also house a webshop selling a wide range of allergy-related products which could help patients to avoid, prevent and relieve allergies. These were not products manufactured by ALK itself, and it represented a new approach for ALK to be marketing allergy products other than its own vaccines and its adrenaline injector. Possible products included salt-inhalers and selected fish oils, nose filters and air purifiers, vacuum cleaners and bed linen.[132]

The concept was that the platform should be the first place allergy patients went to for information, and where they could find relevant products to relieve their allergies. However, the main aim was not to sell products but for ALK to reach allergy-sufferers and offer information and dialogue to help those who needed treatment to get in touch with an allergologist. As such, it was mainly about expanding the market for allergy vaccines – without mentioning ALK's products.

Not everyone within ALK was happy with the concept behind the platform and, in particular, the plan for a webshop met with internal resistance and a fear that the product range would damage the company's reputation and brand as world-leader in the market for immunotherapy treatment for allergy.

This was addressed by management, who emphasised that the platform would promote the branding of ALK as an allergy company rather than a manufacturer of allergy immunotherapy products. The company's allergy vaccines were still its core business, which the platform was intended to help patients with severe allergies to discover and seek treatment with: 'We believe it is a strength of the brand that we now cover more people and either equip them with information about allergy or tell them about treatment options, of which allergy immunotherapy may be one,' explained Mads Lacoppidan.[133]

The platform, including the webshop, was called *klarify* and it was launched in Germany in April 2018 on the company's existing German website, *allergiecheck.de*, which already had almost two million unique users. Five months later, the platform went up in the UK, and by the end of the year around fifty allergy-related products in ten categories were on sale in the webshop.



ALK's digital allergy platform, klarify, was launched in Germany, in April 2018, and has since been extended to a number of other markets.

While Germany was ALK's biggest market, allergy vaccines were less widely used in the UK, and the plan was to run *klarify* in the two very different markets and gather experience before rolling the platform out further.

The same approach was taken with the launch of another digital tool for allergy-sufferers, when a *klarify* app for smartphones was introduced in Germany in April and subsequently in the UK. The app carried the latest local pollen counts and other relevant figures, so allergy-sufferers could take precautions and plan the day's activities. In October 2018, *klarify* won an award in Germany for the best health app.

Growing success for tablet-based vaccines

When the growth plan was published, ALK had indicated that 2018 would be the worst of the three-year transformation, with revenue likely to fall by DKK 200 million. However, the performance was better than expected with revenues of DKK 2.915 billion representing a very modest increase of DKK 50,000.

This success came in spite of the phasing out of a large number of preparations as part of the general product rationalisation and the PASS project, which hit the German market particularly hard. However, the fall in income was not immediate, as the company continued to supply existing patients with preparations for the remainder of their treatment.

This success in the face of the phase-outs was down to a 30 per cent growth in tablet sales, which now accounted for 23 per cent of the company's total revenue, while the other products were losing ground. To promote this development, a greater focus was placed on tablet sales with an update to the strategic plan, whereby the goal of completing the portfolio of tablet-based vaccines was supplemented with a goal of commercializing them.

In the USA, sales of tablet-based vaccines rose by 29 per cent – albeit from a low starting point, so the figures were still very modest even though the company had achieved its target of 5,000 new patients being treated with ODACTRA. Around 1,500 American allergologists were prescribing tablet-based vaccines, and the target for 2019 was to bring this up to 2,000: 'The big difference from a year ago is that it seemed then that they didn't want tablets,' said Carsten Hellmann. 'Now they do. There is not the same resistance to a tablet regime that we saw to begin with,' was his optimistic assessment.

However, he stressed that it would be 'a long haul', but if ALK could pick up 10-20,000 new patients for treatment in 2019, the company would make over DKK 100 million in tablet sales in the USA: 'That would be in line with our plan.'[134]

Complete the tablet portfolio and digital initiatives

This progress, and the ongoing transformation of ALK, continued in 2019, as shown by the half-year figures which were published at the beginning of August. Revenue grew by 11 per cent to DKK 1.65 billion, driven by the tablets where sales were up by no less than 42 per cent. There were also prospects of a faster pace of growth after ALK obtained European approval for its tablet vaccine for tree pollen allergy in June 2019 and submitted an application for approval in Canada in the same month.

ITULAZAX was to be introduced in the first European markets in the autumn, when ALK also planned to step up the use of digital tools to support the launch. This would be achieved through interactive use of apps and online tools including learning from user behaviour on the internet, where the company could use its knowledge of purchases made in the webshop to make potential candidates for immunotherapy aware of the possibility of receiving treatment with tablets.

This was the first time that *digital patient engagement* played a serious role in the launch of an immunotherapy product and, 'with the experience we have gained so far, expectations around a product launch are sky-high,' said Carsten Hellmann of the company's online platform, *klarify*, and the *klarify* allergy app.[135]

In the first half of 2019, *klarify* had reached more than 125,000 new downloads, with over 110,000 allergy tests taken in Germany alone, while 40,000 users had used the company's digital tools to search for contact details for an allergologist. In Sweden, 80,000 users had been in electronic contact with the company in the last six months.

The ITULAZAX tree pollen tablet as a new growth driver

The launch of the tree pollen tablet, ITULAZAX, in Germany in September 2019 was ALK's most successful to date, with over 10,000 patients receiving treatment by the end of the year, which helped to bring tablet sales in the last quarter of the year up to DKK 269 million. Over the whole year, total sales of tablet-based vaccines rose by a full 45 per cent to DKK 973 million, while drop and injection-based vaccines and other products stagnated.

Sales were advancing in all regions, with International markets in particular booming with a jump of 112 per cent driven mainly by tablet sales in Japan, but with good performance in other markets too, with China registering double-digit growth for example. Europe saw a 7 per cent increase, while the USA reached 9 per cent with advances for both injection and tablet-based vaccines.

The company's total annual revenue rose by 11 per cent to DKK 3.27 billion, and both operating profit (EBITDA) and free cash flow were much better than expected. The share of the total revenue attributable to tablet sales grew to 30 per cent, and ALK eyed the possibility of tablets surpassing the injection and drop-based vaccines as early as 2020.

Tree pollen tablet for birch pollen allergy.

Anders Hedegaard, Chairman of the Board of Directors at ALK since 2020.

ALK was back on track in terms of growth, and the success of the tablet-based vaccines and the rationalisation of the old product portfolio meant that the company was ahead of schedule in transforming the business. Investors and the equity market were also happy, as shown by a 70 per cent rise in the share price during the year.

The scene was set for a positive general meeting on 11 March 2020 at the company's headquarters in DTU Science Park in Hørsholm, even though the shareholders had not been paid any dividends for the last two or three years – and would not receive any this time either. The company also said 'goodbye and thank you' to Steen Riisgaard, who had given notice in the autumn of 2019 that he intended to step down after eight years as Chairman of the Board of Directors.

Anders Hedegaard was appointed to the Board in his place and elected as the new Chairman by the general meeting. He took over the role in a situation in which ALK was to face new and hitherto unseen challenges of a global nature the very next week.

The coronavirus pandemic, lockdowns and closed borders

In the evening of 20 March 2020, the Danish Prime Minister Mette Frederiksen went on live TV to announce that the government, with the support of all parties in parliament, was instituting a general lockdown, and three days later came a block on entry into Denmark. The reason for these drastic measures was to tackle an outbreak of the novel coronavirus, Covid-19, which had spread from Wuhan province in China to the rest of the world since the end of 2019. The infection was spreading fast and was well on the way to becoming a pandemic.

Denmark was among the first to lock down and introduce entry restrictions, but more and more countries were following suit, with a severe impact on national economies and world trade. As a pharmaceutical company, a key task for ALK during the pandemic and the lockdown was to protect its employees against infection and illness while maintaining the production and distribution of the whole product range in the interests of patients.

As early as February 2020, the company had assembled a Covid-19 task force headed by Research and Development Director Henrik Jacobi, which was to anticipate and avert the consequences if the infection should spread further, so the company was well-prepared, with all decisions taken on the principle of 'safety first'.

In line with the recommendations from the health authorities, all employees who could do so were therefore asked to work from home. In production and other activities that could not be handled electronically, the number of staff was kept to a minimum, and distancing requirements were introduced and hand sanitisers provided. In Denmark a separate canteen was set up for the workers in production.

Of course it was impossible to prevent some employees being infected, but throughout the pandemic ALK did manage to avoid any uncontrolled outbreak in the company, and production and delivery of its products were maintained without any interruptions.

On the other hand, two major clinical trials in Europe and North America on the use of the house dust mite tablet to treat children with allergies in the upper respiratory tract and asthma had to be extended, partly because it was now harder to recruit participants.

A smaller Phase III trial in Vienna treating adult Chinese patients with the house dust mite tablet had to be suspended altogether, but was expected to resume in 2021. This trial was initiated around the end of 2019, after ALK had been told by the Chinese authorities it did not need to run a large-scale Phase III trial in China itself. Instead, the company was to fly 300 Chinese subjects to and from Vienna, where

they were exposed to controlled quantities of house dust mite particles in a special exposure chamber. Not only would ALK save hundreds of millions, but the company also hoped to be able to launch ACARIZAX onto the Chinese market as early as 2023, five years earlier than originally estimated. The coronavirus pandemic and closed borders put a stop to this, as the trial had to be suspended.

Of the two trials in children, the study of allergy in the upper respiratory tract was carried out as planned, albeit with a delay, while the asthma study was cancelled. The reason was that the coronavirus pandemic was proceeding in waves, and the sustained use of protective measures such as face masks and distancing reduced the frequency of viral infections and so also significantly reduced exacerbation of the participants' asthma. A similar reduction in cases of asthma exacerbation was observed throughout society during the coronavirus pandemic.

ALK therefore judged that the trial was unlikely to deliver usable results relating to the effect of the house dust mite tablet on asthma exacerbation cases. It was however convinced that the extended study of allergy in the upper respiratory tract would lead to full paediatric coverage, as practically all children with house dust mite-induced asthma also have allergic symptoms from the upper respiratory tract.

The prolonged nature of the coronavirus pandemic and the recurrent lockdowns and travel restrictions, especially in China, also meant that the 'chamber study' on the house dust mite tablet in Vienna could not be resumed as planned. However, ALK did enter into discussions with the Chinese authorities on its possible continuation and completion, but without getting a definite answer.

'... zero – as in zero – patients'

Like other pharmaceutical firms, ALK benefitted from the fact that patients still needed treatment and had to have their medicines, but the pandemic did have an adverse effect on sales of injection-based vaccines in particular, as lockdowns or the fear of infection deterred patients from finding a clinic to get an injection.

The American market was particularly hard-hit by the pandemic, with up to half of all allergy clinics partly or completely closed at one point, and a lot of patients were staying away: 'In the first six or seven weeks of the quarter, there were zero – as in zero – patients going to their doctors. They weren't going to the pharmacies either,' said Carsten Hellmann of the reason for the sharp drop in sales of tablet, injection vaccines and allergens in the first quarter: 'There was nothing we could do about that, and in that situation it is obvious that we will lose sales.'[136]

Sales did recover in the second half of the year, but not enough to prevent revenues in North America falling by 10 per cent in 2020 to DKK 573 million.

In Europe, on the other hand, the trend was positive with growth of 8 per cent, although the injection business was hit by the pandemic here also – but this was more than offset by strong growth in sales of tablets.

International markets excelled once more with growth of 58 per cent to DKK 368 billion, with Japan and China the strongest performers with growth of 80 per cent and 28 per cent respectively; the gains in Japan were made up of royalties and supplies of tablets to Torii.

Success in the face of the coronavirus pandemic

Despite the coronavirus pandemic and the difficulties in the USA, 2020 as a whole was a good year for ALK financially, with revenue increasing by 8 per cent to just under DKK 3.5 billion. This was at the low end of the published expectations, but clearly attributable to the pandemic, which cost the company more than DKK 100 million in sales in the USA alone, equivalent to almost 3 per cent of the company's total revenue. Added to this was the effect of phasing out older products, which reduced growth by 4 per cent.

The overall growth was driven by tablet sales, which grew by 42 per cent and proved to be largely unaffected by the pandemic as the

In the course of the year, half a million people had taken an allergy test via ALK's digital platforms, and the company had more than 475,000 'two-way relationships' with consumers. Around 140,000 people had been motivated to do something about their allergy.

tablets could be taken at home. Operating profit (EBITDA) grew by 64 per cent to DKK 395 million, and for the first time since 2016 the bottom line moved into the black with a modest pre-tax profit of DKK 25 million and free cash flow of plus DKK 56 million.

A crucial factor in this positive trend was the strong momentum behind the growth in sales of tablet-based vaccines, which may also have had something to do with the coronavirus pandemic in the sense that this had prompted the company to speed up the expansion of its digital tools. For example, the *klarify* allergy platform had been rolled out further and was now available in the USA, Denmark, Ireland and Slovakia as well as Germany and the UK: 'We can see that we are exceeding our own targets and all of our expectations, ' said Carsten Hellmann at the end of the year. 'We were doing that before Covid, but now we are doubling what was already doubled. I am firmly convinced that Covid has had a positive effect for us when it comes to online activities.'[137]

In the course of the year, for example, half a million people had taken an allergy test via ALK's digital platforms, and the company had more than 475,000 'two-way relationships' with consumers. Around 140,000 people had been motivated to do something about their allergy: 'These are very big numbers that we now have in our *klarify* universe. Are they also because of coronavirus?' was the rhetorical question from Carsten Hellmann, which he answered himself: 'Yes, I think they are.'[138]

The webshop also had a bit of progress, although the revenue was still modest – 'no big double-digit amounts' according to Hellmann, as there were no exact figures.[139] And the main purpose of the webshop was not to make direct sales but to act as a screening tool to help more patients to obtain treatment with allergy vaccines. At that time, the webshop was already being replaced by the idea of *klarify* as the key digital screening tool, so the webshop was being phased out and had no more sales anyway.

Targets exceeded

The annual accounts for 2020 were a fitting conclusion to the three-year growth strategy, and all in all, the Chairman Anders Hedegaard and CEO Carsten Hellmann were well pleased when the annual report for 2020 ran the rule over the three-year transformation of ALK, in which all of the financial goals had been surpassed:

- The cumulative revenue was DKK 700 million better than expected
- The cumulative operating profit before depreciation and amortisation was DKK 800 million better than expected
- The cumulative free cash flow was DKK 700 million better than expected

As for the objectives for the four key areas of the growth plan, all had been achieved apart from the ambition to break through with the tablets in the USA. However, the company had established an infrastructure and launched the house dust mite tablet in the USA and Canada and had created a base of American allergologists who were prescribing tablets. Its failure to reach the target of 10,000 new patients receiving tablet treatment in 2020 could be largely blamed on the coronavirus pandemic, but Hellmann also acknowledged that they had underestimated the aversion of the American allergologists to tablet-based treatment.

The company had achieved its target for allergologists writing prescriptions for tablets – the problem was that most of them were writing very few: 'When they are making one or two million dollars a year from mixing their own injection-based vaccines in a back room, it's hard to get them to give up their business and go for tablets instead,' said Hellmann.[140]

As for completing and commercialising the range of tablets, the launch of the ITULAZAX tree pollen vaccine tablet had brought the company to its goal of a complete portfolio to treat five of the most common allergies. With average annual growth of 37 per cent, the tablets had also become the primary growth driver. On the other hand, the pandemic had delayed or stopped the clinical trials in children that were meant to result in child and asthma indications, and the Chinese chamber study in Vienna had been suspended.

The use of the internet and digital tools to strengthen contact and dialogue with allergy-sufferers had taken off with the launch of the *klarify* allergy app and the roll-out of the company's digital platform, *klarify.me*, in six countries.

Finally, there had been a comprehensive upgrade and quality assurance of all production facilities, and around 300 older product variants, or 60 per cent of the total product portfolio, had been phased out. The PASS project had also made 3,500 upgrades to older preparations to comply with the quality and documentation requirements from the authorities.

A changing culture

There had also been noticeable progress in the efforts to bring about a culture change in the company. With the aim of placing the patient centre-stage and helping more and more people to receive treatment for their allergies, both ALK and the individual employees had adopted a shared overall goal.

This view was reinforced when ALK signed up to the UN Global Compact principles and adopted a strategy in 2020 entitled *Access to Allergy Care*, which identified the work of improving access to medical treatment and helping as many allergy patients as possible as a core priority.

This strong focus on helping patients was also reflected in the interim and annual reports, in which the company no longer showed just the financial indicators but also the number of patients who had been helped to obtain treatment with the company's products. In 2022, this ran to 2.4 million people – a net growth of 300,000.

With the overarching focus on the patient as the guiding lighthouse, the three cultural beliefs formed the basis for the company's growth and development, as they now permeated the whole organisation and its day-to-day work across departments and functions and within individual work areas. They were also incorporated into training programmes for both managers and other employees, while

Employees at ALK's headquarters in Hørsholm, north of Copenhagen.

new staff were introduced to the core values from the outset and told how the company applied the three cultural beliefs. To further reinforce the corporate culture change, 150 managers were also trained in the use of agile tools and processes.

The three cultural beliefs were also included in the annual staff appraisals, and used as a parameter in the overall assessment of individual employees.

These targeted efforts towards a culture change brought perceptible progress, even though the results were not measurable in the same way as growth in revenue and profits. Nevertheless, the findings from the annual employee engagement and satisfaction surveys showed a positive trend.

Lisbeth Kirk,
Senior Vice President, HR,
Sustainability & Internal
Communications since 2019.

The survey in the autumn of 2022 was answered by 95 per cent of all employees – a record response rate after a rise of 2 percentage points from the previous year. An even more telling indication of growing employee engagement with the company was that more than 11,000 comments were received from the 2,600 or so employees who responded, giving a valuable insight into what the company should go on doing and what could be improved.

Overall, the survey returned a commitment score of 8.3 on a scale from 1 to 10, which took ALK from 25th to 5th place among similar pharmaceutical companies participating in the survey.

The Director of Human Resources, Internal Communications & Sustainability, Lisbeth Kirk, was also very happy with this trend: 'We have come a long way,' she said, while emphasising that the company had not yet reached its goal. And she added that, in a sense, it never will: 'Work on the corporate culture is a constant process, because the world and the company itself are changing all the time. There is no final destination.'[141]

'Work on the corporate culture is a constant process, because the world and the company itself are changing all the time. There is no final destination.'

Lisbeth Kirk, Senior Vice President, HR,
Sustainability & Internal Communications

ALK's headquarters in Hørsholm, north of Copenhagen.

9.

Stable growth, increasing profitability and future growth drivers

ALK at a turning point

After the successful execution of the three-year growth strategy, the main task for ALK was to sustain the results achieved so far and use them as a platform for continued success in its efforts to become the allergy company. The company's overarching strategy for the next three years from 2021-23 was unchanged in the sense that it would still be rooted in the four key areas, but with a number of adjustments and updates.

Financially, the objective was to maintain stable and sustainable growth of 10 per cent a year and to generate increasing profitability with the ambitious target of an EBIT margin of 25 per cent in 2025. This was equivalent to a sixfold increase in the EBIT margin compared to 2020, when it had been a touch over 4 per cent.

The reason for using EBIT (earnings before income and taxes) as a measure of the company's long-term profitability was that the focus was now on the core business, and that the costs in the next phase would be lower and more stable – although there would still be significant expenses for clinical trials, with the aim of securing paediatric indications for all tablets.

With these new financial targets, the updated strategic plan marked a turning point brought about by the successful turnaround over the past three years. Since its independence from Chr. Hansen in 2004 and up to the completion of the growth strategy in 2018, ALK had never been really profitable. It was the milestone payments from Merck and Torii and others that had provided the regular operating profits, and without them the company would have been barely sustainable.[142]

So ALK had been short of financial resources for the whole period, and this had limited its options. This was particularly clear from the fact that almost ten years had elapsed from the launch of GRAZAX before the company could claim what Søren Jelert, the Chief Financial Officer since January 2018, called 'a meaningful portfolio of tablets.'[143]

That time was now past if the company wanted to be able to maintain its momentum, as the results in 2021 clearly showed it could.

Søren Jelert, Chief Financial Officer from 2018-2023.

Revenue grew by 12 per cent to almost DKK 3.9 billion, while operating profit (EBITDA) increased by 35 per cent to DKK 534 million. Tablet sales were once again the principal growth driver with an increase of 29 per cent, which meant that income from the tablets accounted for 45 per cent of the company's total revenue.

ALK was still modest in size, but the growth in revenue and increasing profitability provided the financial scope for new initiatives and investments with the aim of strengthening its efforts within the four key areas, and also of developing new business areas and technologies to create the growth drivers of the future. This was a process that had got underway during the three-year growth strategy but was now accelerated.

Digital access and new initiatives in the USA

Despite the aversion of American allergologists to the tablet-based vaccines, ALK had not given up its ambition to conquer the American market. This objective was retained, but the strategy was modified so, instead of focusing on the allergologists, the company would now take the opposite tack and encourage the patients to put pressure on their doctors to provide treatment with tablets. This would happen via the digital platform *klarify*, where ALK could make direct contact with the patients, encouraging them to consult a doctor about their allergy, while also working to ensure the tablets were available from the major pharmacy chains so their prescriptions could be easily fulfilled if their doctor prescribed ALK's vaccine tablets.

Another initiative was to get other doctors than allergologists to prescribe the company's vaccine tablets. With this in mind, ALK had entered into a partnership agreement in June 2020 with the American biotech and pharmaceutical company, Otonomy, whereby ALK was granted exclusive rights to market the OTIPRIO product to American ear, nose and throat (ENT) specialists.

OTIPRIO was used to treat acute ear infections, and so completely unrelated to ALK's existing product portfolio, but the agreement enabled ALK to get in touch with American ENT specialists, more and more of whom had started to treat allergies and write prescriptions for ALK's tablets.

Altogether there were around 13,000 ENT specialists in the USA, almost three times the number of allergologists, which made them 'the second largest group in the USA after the allergy doctors that we want to focus on,' explained ALK's Executive Vice President, R&D, Henrik Jacobi. 'They already account for a large part of our revenue and have been the fastest-growing new segment for our American business.' In August 2021, ALK went the whole way and bought all of the rights to OTIPRIO.[144]

There were also great expectations within ALK regarding the effect of the 'child' indications for the tablet vaccines, as they would then be of interest to American paediatricians. GRAZAX had already gained a paediatric indication, and in April 2021, the ragweed tablet,

An employee collecting catkins from ALK's birch tree plantation in Post Falls, Idaho, USA.

ALK's production site in Post Falls, Idaho, USA.

RAGWITEK, was also approved by the FDA for the treatment of children.

ALK was also running a major Phase III trial of ODACTRA/ACARIZAX in the USA and Europe, which was expected to finish at the end of 2023 and where the company had high hopes, as positive results would mean that all of the company's tablets on the American market were approved for all age-groups.

Another initiative to provide ALK with a wider presence in the American market was taken when ALK entered into an agreement in August 2019 with the US pharmaceutical company, Windgap Medical, to develop an adrenaline pen to treat anaphylactic shock. The agreement gave ALK the global sales and distribution rights in return for milestone payments and royalties.

An immediate aim was to establish ALK in the market for adrenaline pens in the USA, where around 200,000 people suffered anaphylactic shock each year. According to the *Asthma and Allergy Foundation of America*, more than 16 million Americans experience anaphylactic shock at least once in their lives.

However, a new product generation was needed to penetrate the American market, not least because a number of similar products to the existing benchmark had become available. Windgap's pen was based on a wet/dry technology where the adrenaline dose was dry until it was mixed with the wet ingredients at the moment when it was used. This was designed to give it better temperature stability and extended shelf-life, and it was designed to be smaller than existing pens.

ALK also started to develop its own adrenaline pen based on its experience with JEXT, which had a strong position in Europe but was not sold in the USA. So the company was backing two horses by investing hundreds of millions of kroner in its own development in parallel with the Windgap project.

'We will be running both projects and continuing to invest heavily in both in 2022, ' said Hellmann in November 2021. 'We *want* to have a product on the American market which can then be further developed for the Chinese market – that is a *given*, and that is why we have no reason not to cover ourselves *big time*.'[145]

At the same time Hellmann made it clear that ALK would choose one of the two products in the not-too-distant future and take it forward into the registration process, given the substantial costs of having two projects on the go. However, he did not reveal which way the company was leaning, but promised that 'whatever happens, we will have submitted an application by 2024.'[146]

China as a future growth driver

Carsten Hellmann's reference to China arose from the thought that not just the new adrenaline-pen, but also the Chinese market were seen as future growth drivers for the company's products. In 2018, ALK had therefore entered into an agreement with a Chinese firm, Rellergen Biotech Inc., which gave the Danish company exclusive rights to market Rellergen's Bio-IC technology for diagnosing allergy in more than 190 hospitals all over China.

This was followed in July 2021 by an agreement on JEXT, which gave the Chinese pharmaceutical firm, Grandpharma, exclusive rights to launch and sell the adrenaline pen in China, where there were no other products on the market. The initial launch would be in southern China, based on the existing approval of the product in Hong Kong, where it could start immediately thanks to a special import regulation.

Under this agreement, Grandpharma, which was China's leading importer of adrenaline ampoules, and well represented in clinics and emergency rooms, would then handle the approval, import and sales of the pen in the rest of China plus Macao and Taiwan. ALK would supply the product and provide marketing support based on its experience in Europe and other markets, and would receive an up-front payment of DKK 90 million with subsequent milestone payments and royalties.

ALK was already marketing the injection vaccine, ALUTARD, for house dust mite allergy, and the skin prick test product SOLUPRICK

SQ, which had been enough to deliver double-digit growth rates in recent years. The launch of JEXT was expected to take this further.

And there was more on the way. At the beginning of May 2022, ALK announced that the Chinese authorities had issued a dispensation allowing the company to submit its application to register ACARIZAX without a prior Phase III clinical trial. So the interrupted chamber study in Vienna would not resume, and the application would instead be based on ALK's European data, after the company could then gather Chinese data once the preparation had come onto the market.

China was the world's second-largest market for the treatment of house dust mite allergy, with a potential far exceeding the existing sales of immunotherapeutic vaccines. ALK was already making good progress with a 40 per cent growth in sales of ALUTARD in 2021, which the company planned to accelerate as it built up and expanded its Chinese organisation.

Given that ALK could likely launch the first – and only – tablet vaccine against house dust mite allergy in China earlier than expected, there was the further prospect of attaining a unique position in a large and growing market, which the company was putting a huge effort into as one of its future growth drivers.

Peanut allergy – a new business area

The work of developing new growth drivers also took ALK into a new business area which it had previously had little to do with. In its annual report for 2020, published on 10 February 2021, the company announced its intention to enter the food allergy market, which was a new business area but closely linked to its existing activities. The measure was therefore in line with the ambition to turn ALK into *the* allergy company and the obvious partner for allergy-sufferers – an ambition that had so far only covered people with respiratory allergies.

In the first instance, the company would try to develop a tablet for peanut allergy, which was a big thing in itself, with an estimated 2.5 million children affected in the USA and Europe. Then the company could focus on nuts, followed perhaps by milk and eggs.

The announcement came a few months after the world's largest food and drink group, Nestlé, had paid USD 2.6 billion for the US company, Aimmune Therapeutics, which had obtained approval in the USA for its peanut allergy treatment, Palforzia, back in January 2020. At the end of the year it was also approved in the EU.

And the French firm, DBV Technologies, which ALK had a stake in back in 2009-13, was still working on the vaccine plaster for peanut allergy, called Viaskin. The FDA had refused US approval as recently as August 2020, but this did not cause the company to abandon the project as it still hoped to launch within 2two or three years.

This was a time frame that ALK could not match, but it was Palforzia, with its FDA approval and Nestlé's global position, which was a real competitor. ALK was trailing, but this did not frighten Carsten Hellmann, who said of the competition that 'they may be the first but it is far from certain that they are the best.'[147]

Palforzia also had a number of serious side-effects – for example, 14-15 per cent of the subjects who took the preparation in the Phase III trials had a serious allergic reaction, against just 6 per cent in the

Laboratory technician Sebina Krogdal Muhs at work in ALK's laboratory in Hørsholm, Denmark.

control group taking placebo. The preparation also required a very long course of treatment with a total of 16 fortnightly visits to an allergologist, including an hour's observation each time in case the patient went into shock.

It was different with Viaskin, as the preparation had a good safety profile which prompted the FDA to ask BDV to rethink its plaster technology to improve the uptake of allergens, and to carry out fresh Phase III trials.

Neither Viaskin nor Palforzia was designed to cure peanut allergy, but only to protect the patient by enabling them to tolerate the effect from peanuts and reduce the allergic reactions and ultimately minimise the risk of anaphylactic shock.

ALK took the same approach, and the aim was to develop a peanut tablet to be placed under the tongue, but with greater efficacy than Viaskin and a much better safety profile than Palforzia. In the autumn of 2021, a *feasibility study* showed that the company's fast-dissolving tablet technology could be used to develop a peanut allergy vaccine, and after acquiring the right to use this technology which had been developed by Catalent, ALK kicked off clinical Phase I trials in the summer of 2022, which were expected to finish the year after.

In the same autumn, the FDA brought a temporary halt to BDV Technologies' development of Viaskin, ordering a change to the design of the Phase III trial – but the French company did not give up. A few months later, Nestlé announced that Palforzia was to be sold off, as it had not lived up to expectations.

However, another competitor, the UK-based Allergy Therapeutics, announced that it had raised DKK 141 million to fund a Phase I clinical trial of a vaccine against peanut allergy and to finance the subsequent Phase II and part of an expected Phase III trial.

The race was on.

New technologies

While the efforts to develop a preparation against peanut allergy were based on ALK's existing tablet technology and natural allergens, the company also took an initiative to develop other, new technologies within allergy treatment. At the end of 2019, the company entered into a research partnership with the US biotech company X-Chem covering drug discovery and preclinical research into new medicines to treat allergies.[148]

Where ALK worked with organic substances and large molecules, X-Chem worked with small molecules, and the company's contribution to the collaboration was its technological platform, a 'DNA-encoded library' (DEL), where screenings could be run to identify potential drugs. ALK brought its scientific expertise in allergies and immunology and its experience of developing immunotherapeutic medicines against allergy.

The purpose of the agreement was not to develop new drugs to replace the existing product portfolio but to use early research to strengthen the company's R&D pipeline with complementary preparations alongside the existing portfolio, which could use new technologies to help allergy sufferers: 'Completing and commercialising the product portfolio remains the primary focus of ALK's research and development,' said Henrik Jacobi, stressing that it would be a long time before the collaboration with X-Chem would yield any results in the form of new drug candidates.[149]

ALK at a glance

On 3 February 2023, ALK published its annual report for 2022, which showed that the company was still on a growth path. Revenue was up 13 per cent to a record DKK 4.5 billion, on the back of growth in all regions and all product lines. Tablet sales grew by 18 per cent and now made up 46 per cent of the company's total revenue. Operating profit (EBITDA) of DKK 708 million also set a new record after growth of 33 per cent. The headcount had also increased to 2,609 employees, 200 more than when the growth strategy was launched in January 2018.

Leadership in the global allergy vaccine market

These figures strengthened ALK's position as the world's undisputed leader in the production of allergy vaccines. The only challenger, Stallergenes Greer, which had been marginally bigger than ALK in 2015, had fallen back both in terms of revenue and in the development of new tablet vaccines. A contributory factor was the enforced closure of the company's production in France at the end of 2015, which took until 2021 for the company to recover from.

Since all of Stallergenes Greer was taken over by the investment fund, Waypoint Capital, in 2019, the company had not published any figures, but analysts estimated from other sources that revenue in 2021 came to EUR 327 million, or just under DKK 2.5 billion – 36 per cent below ALK's total of around DKK 3.9 billion.[150]

On the product side, Stallergenes Greer was still selling mainly drop-based vaccines and, to a lesser extent, injection vaccines, while the company had just two vaccine tablets in its portfolio against ALK's five. Of Stallergenes Greer's two tablets – for grass pollen and house dust mites, respectively – the latter only obtained European approval in May 2021 and was still awaiting approval in the USA at the end of 2022.

So while ALK now increasingly led the way in the global allergy market, Stallergenes Greer seemed to be no more than a shadow of its former self compared to the years when the two companies were competing on level terms on both revenue and products.

All in all, ALK's position as global market leader looked untouchable as, apart from ALK and Stallergenes Greer, there were only national or regional producers with predominantly non-registered products. Nor was there any danger of external threats from generic products, even though the company's preparations were not patent-protected.

As ALK's vaccine tablets are not based on small molecules but on complex extracts, they could not be directly copied, and if any new players should try to push into the market for allergy vaccines, they would have to go the whole way from manufacturing and processing

‘Completing and commercialising the product portfolio remains the primary focus of ALK’s research and development.’

Henrik Jacobi,
Executive Vice President, Research & Development,
from 2003-2023

Employees at work at ALK's production site in Hørsholm, Denmark.

raw materials to developing preparations with clinical trials in all three phases. Then would come the registration processes, before regulatory authorisation can be granted. As ALK found, this is a process that can take up to ten years, which was unlikely to tempt anyone – not even the very large global pharmaceutical giants – given the size of the markets.

Over the years there had been countless attempts to produce allergy vaccines from peptides or through gene-splicing, but all of them had failed.

Driving creation and change in the allergy vaccine market

For the moment, then, and at the time of publishing this history, ALK has the global allergy market largely to itself – and hence big potential sales still to look forward to. On the other hand, the absence of competitors also means that the company is on its own in developing the markets and modifying the surrounding infrastructures to allow only evidence-based and approved preparations to be used.

This is a long and tedious process, but the example of Germany shows that it can be done, as the country's health authorities issued new national guidelines for reimbursement payments at the end of 2020 and recommended that new treatments for allergy should only start with registered products. These were the sort of regulatory changes that ALK had been working for since the start of the Allergy unlocked campaign in 2014, and Germany now stands as an example to other European countries where there has been a similar development over many years driven by the authorities' demands for documentation of the efficacy of the medicines they are granting reimbursement for.

Despite its small size, and despite all the challenges in the years since the launch of GRAZAX, ALK has been a driver behind this development and has managed to set a new agenda for the creation of a global allergy vaccine market built on evidence-based and officially approved medicines. Among the vaccine producers, there is no doubt that ALK has set the pace in transforming the allergy vaccine market into a regular pharmaceutical market with the same ground rules as other medicines.

And ALK is still moving forward – most recently with the publication of the results from a large *real-world evidence* study at the end of 2021, with more than 92,000 patients, making it the largest of its kind. This study covered the effect of the house dust mite, grass and tree pollen tablets and documented the effect of these preparations out in 'the real world' as opposed to in organised clinical trials.[151]

The results were encouraging as they showed, along with the long-term effect, that patients with asthma who received allergy immunotherapy were more inclined to step down their asthma treatments and were less likely to step them up again. They also found a preventative effect on serious asthma exacerbations and cases of pneumonia.

The results were vital to ALK, as there was a increasing tendency in both the USA and Europe to supplement the traditional clinical trials with *real-world evidence* studies comparing a new treatment with the existing standard of care – and here the study hit the mark: 'The essential value of allergy immunotherapy is the disease-modifying potential of the treatment and particularly its ability to have a long-term effect even after the treatment has finished,' said Henrik Jacobi.[152]

Out of the niche

The development of the first allergy vaccine tablet, GRAZAX, came out of a realisation within ALK in the 1990s that allergy vaccination was a niche treatment covering a small part of the large group of allergy-sufferers who ought to be receiving treatment.

The two crucial factors in changing this and emerging from the niche were that ALK focused both on producing better and better documentation of the advantages of allergy vaccination and on developing more user-friendly vaccine methods, which led to the launch

of GRAZAX in 2006, with the further aim of building up a portfolio of tablets covering the commonest allergies, which is now a reality.

The work of documenting the efficacy of allergy vaccination and the benefits of this treatment is still going on, with the spotlight now turned on the company's five tablet-based vaccines for grass, tree pollen, house dust mite, ragweed and cedar wood allergies. The result is that ALK now has a solid and well-documented portfolio, which will be able to drive the company's growth and the expansion and development of the global market for many years to come.

The company has also initiated development projects to support further growth in the future: the paediatric indications, with two Phase III trials due to complete in 2023; the two adrenaline pen projects; a peanut allergy tablet as an initial step into the food allergy market; and, last but not least, the impending launch of the house dust mite tablet in China, after an application for registration was submitted at the end of 2022. A month later, ALK made the tablet available in China's Boao Lecheng *Medical Pilot Zone*, to allow the company to gather feedback and knowledge from patients and doctors ahead of a nationwide launch.

The paediatric indications, the adrenaline pen and the peanut tablet are also expected to support developments in the USA, where the tablets are still registering weak growth, and which remains one of the biggest challenges facing ALK: 'The USA is the largest market in the world, and we cannot be a global player and a long-term operator if we do not break through in the USA – and we are nowhere near getting to grips with this,' says the Chairman of the Board of Directors, Anders Hedegaard: 'This is a major item on the Board's agenda.'[153]

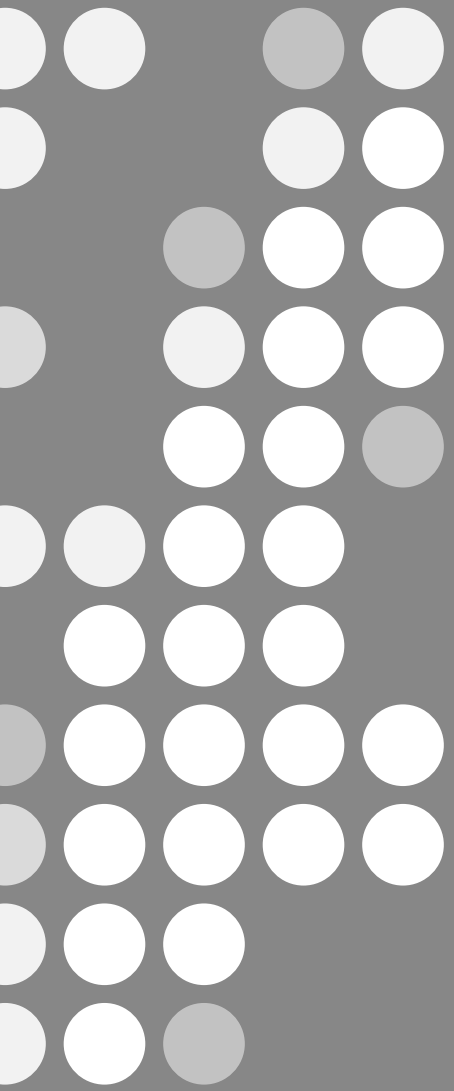
Finally, India emerged as one of the possible future growth drivers after ALK announced in May 2022 that it had entered into an agreement with one of the country's largest pharmaceutical companies, Dr. Reddy's Laboratories, to register and market the house dust mite tablet ACARIZAX in India. The agreement is modelled on the agreement with Torii in Japan, and the expectation is that sales of the tablet could start in 2025 or 2026.

Despite ALK's complete tablet portfolio, and despite the now comprehensive documentation of the efficacy and benefits of the tablets, the fact remains that only a modest number of people with allergy in need of treatment with allergy vaccines are actually receiving any.

Within ALK, people therefore still talk about emerging from the niche – or more accurately coming right out of it, as it finally believes it is. The market potential remains both huge and largely untapped, and ALK remains a small company. With its digital tools, the company has however created a platform that can reach out to allergy-sufferers all over the world, while the tablet portfolio offers evidence-based and approved preparations that are uniform and can be marketed everywhere.

After the many tough years following the launch of GRAZAX in 2006, until the whole tablet portfolio was finally on the market, and after a successful turnaround in 2018-2020 and record-breaking figures in 2022 ahead of its centenary year, ALK finally seems close to realising its ambition from the 1990s: To come out of the niche.

Over the years, ALK has developed a portfolio of standardised and registered vaccines for grass pollen, tree pollen and house dust mite allergy, together with an adrenaline pen for the prevention of anaphylactic shock, and diagnostic products for skin prick tests. Shown here are a number of former and current products and packaging.



Notes

Notes

1 K.H. Baagøe: Allergiforskning i Danmark. Historisk Tilbageblik (1920-1970) (Allergy Research in Denmark: A Historical Retrospective (1920-1970), p. 90.

2 Ibid.

3 Kaj Baagøe and P.C.T. Barfod: Fremstilling af danske Præparater til Kutan-Reaktioner (Production of Danish Preparations for Cutaneous Reactions), pp. 2-3.

4 Farmacevtisk Tidende, (Pharmaceutical Times) 1910, p. 454.

5 Information about Peter Barfod: De Danske Apotekers Historie (The History of Danish Pharmacies), Vol. IV, pp. 376-378. The old hospital apothecary, which was licensed to a private chemist, did not move with it but remained as a private chemist on Bredgade. Instead, the Rigshospital was given a 'dispensation institution', which under the new Chemist Act became a hospital chemist in 1913.

6 DAK is an abbreviation for Danmarks Apotekerforenings Kompositionsudvalg (The Danish Pharmaceutical Association Composition Committee).

7 The feud (from their respective angles) is referred to in V. Christophersen: Den Almindelige Danske Lægeforening 1857-1932 (The Danish Medical Association 1857-1932), pp. 172-173 and Danmarks Apotekerforening 1844-1944 (Danish Pharmaceutical Association), p. 334-339.

8 An article by Chandler Walker and June Atkinson about the results of such experiments, published in The Journal of Medical Research July 1918, is contained in Baagøe's collection of scientific articles in ALK-Abelló's historic archive. Baagøe's own notes are found in a notebook, which also contains recipes for extracts. The notebook is stored in ALK-Abelló's archive.

9 Peter Barfod: Biography of 13 July 1928, The College of Heralds.

10 As per his doctoral thesis: Kaj Baagøe: Bidrag to Studiet of Asthma særlig hos Børn. (Contribution to the Study of Asthma, particularly in Children).

11 Kaj Baagøe: Bidrag to Studiet of Asthma særlig hos Børn. (Contribution to the Study of Asthma, particularly in Children).

12 Suzanne Gravesen and Carsten Schou: Allergi og anden overfølsomhed (Allergy and other oversensitivity), p. 12. Kaj Baagøe: Allergiforskning i Danmark (Allergy Research in Denmark), p. 91. See also his presentation in: Kaj Baagøe: Opening Speech at the First Northern Congress of Allergy, September 9-10, 1947, p. 125.

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Foreword.

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19 Proclamation of Mr. P.C.K.T. Barfod as Knight of the Dannebrog, 13 July 1928, The College of Heralds.

20 The merchant and pharmacist Paul Tjellesen, who became a 'disciple' at the Frihavn Chemists in 1930. Farmaci (Pharmacy) No. 12, 2002, p. 22. Further information: Peter Clemmensen: K.V. Tjellesens historie (K.V. Tjellesen's Story), p. 10.

21 Note inserted in ALK-Abelló's archive. Katalog over Frihavns Apotekets præparater (Catalogue of the Frihavn Chemist's Preparations), also in Alk-Abelló's archive.

22 Ibid.

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96 Medwatch, 3 December 2015.
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103 Medwatch, 23 February 2016.
104 ALK press release, 26 July 2016 and Medwatch, 4 August 2016.
105 Medwatch, 27 July 2016.

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112 Ibid.
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114 Ibid.
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122 Interview with Christian Houghton, 11 October 2022.
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129 Ibid.
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133 Medwatch, 26 February 2018.
134 Ibid.
135 Medwatch, 13 August 2019.
136 Medwatch, 12 August 2020.
137 Medwatch, 12 November 2020.
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139 Ibid.
140 Medwatch, 12 February 2021.
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152 Ibid.
153 Interview with Anders Hedegaard, 27 January 2023.

ALK milestones through the first 100 years

1923
Doctor Baagøe and pharmacist Peter Barfod produce the first pharmaceutically manufactured allergen extract at the Copenhagen University Hospital
Page 19 →

1928
Peter Barfod starts pharmacy production of allergy immunotherapy treatment
Page 27 →

1972
ALK develops a technique (CRIE) to accurately identify the proteins that provoke allergies
Page 40 →

1976
ALK develops the first standardised process for manufacturing allergen extracts
Page 46 →

1978
The world's first standardised allergy immunotherapy, ALUTARD SQ®, is launched by ALK (Grass pollen, Tree pollen, House dust mites, Animal hair and dander, Bee and Wasp venom)
Page 50 →

1990
ALK introduces the world's first sublingual allergy immunotherapy drops: SLIT-drops
Page 74 →

2001
ALK introduces the sublingual allergy immunotherapy (SLIT) tablet-pipeline
Page 80 →

2005
First SLIT-tablet trial to demonstrate clinical efficacy in allergic rhinitis (GRAZAX®)
Page 82 →

2006
GRAZAX® – the world's first SLIT-tablet is launched in Europe
Page 86 →

2008
The first SLIT-tablet trial to demonstrate clinical efficacy in allergic asthma (ACARIZAX®)
Page 102 →

2009
ALK's new headquarters in Hørsholm is inaugurated
Page 107 →

2010
ALK launches JEXT® Adrenaline Autoinjector
Page 121 →

2014
GRASTEK®
ALK's tablet against grass pollen allergy is launched in the USA
Page 124 →

RAGWITEK®
ALK's tablet against ragweed allergy is launched in the USA
Page 125 →

2015
ACARIZAX® – against house dust mite allergy is the world's first SLIT-tablet to be approved for both allergic rhinitis and allergic asthma. In Japan the product is launched under the name MITICURE®
Page 127 →

2016
ACARIZAX®
ALK's tablet against house dust mite allergy is launched in Europe and Australia
Page 131 →

The GRAZAX® Asthma Prevention (GAP) trial demonstrates that GRAZAX® reduces the risk of asthma symptoms in children with allergic rhinitis
Page 129 →

2017
For the first time, allergy immunotherapy is recommended as a treatment option in the Global Initiative for Asthma (GINA guidelines), based on data for ACARIZAX®
Page 151 →

2018
ODACTRA®
ALK's tablet against house dust mite allergy is launched in the USA
Page 160 →

ALK's consumer universe, klarify, is born to help people with allergy
Page 167 →

2019
ITULAZAX®
ALK's tablet against tree pollen allergy is launched in Europe
Page 171 →

2021
ALK announces an entry into food allergy treatment and begins developing a tablet against peanut allergy
Page 194 →

2023
ALK turns 100 years!
We have been pioneers in fighting allergies for 100 years… and counting. Our purpose is to continue helping people with allergies in many years to come
Page 207 →


years and
counting


years and
counting