Life and Work in the Evolutionary Pharma Industry besity Pharmacotherapy: New Era, New Opportunities?

My life before the pharmaceutical industry is mainly connected to Oldenburg, the center of an agricultural region in Northern Germany. During the time of my birth, my parents were living in Wilhelmshaven, the biggest Naval Port in the North. However, the big battleship Tirpitz was still being equipped there and the Britons tried to drop some explosives quite early in the war. My parents thus felt that Oldenburg was a safer place for being borne. Later in the war, around the production of the US movie "Memphis Belle," which participated in raids over Wilhelms-haven, ca. March 1943, my mother moved with her two kids to Oldenburg. I attended regular schools there after the war, developed my interest in photography, construction of radios and amplifiers, and my favorite school topics like French, physics and chemistry. My studies in chemistry, physics, physiochemistry and microbiology were held in Goettingen. Inevitably, I developed skills in handling most of the machine tools available in the decent mechanical workshop of the organic chemical laboratory, where I could construct two model ships (5-mast-full-rigger Preussen and a Spanish galleon) and some equipment for close-up photography with my Leica.

My life in the pharmaceutical industry began in early 1967. Since Bayer (at that time still called "Farbenfabriken Bayer AG") was in the process of completing a brand new Chemical Laboratory for their Pharmaceutical Branch, I was hired and given permission to stay another 6 months at U. Goetingen in order to complete some synthetic work following my earlier work in the synthesis of cyclohexapeptides, the topic of my thesis completed early 1967. Peptides in general did not play an important role as active ingredients of drugs at the time, but there was optimism that this could change in the not too distant future. Following the classical peptide synthesis of the nonapeptide oxytocin by Vicent du Vigneau (Noble Prize 1955), the '60s saw two important events in peptide chemistry:

1. The ingenious method of Solid Phase Peptide Synthesis (SPPS) developed by Bruce Merri-field in 1963 (Nobel Prize 1984), first applied in the synthesis of a tetrapeptide. This method was used to synthesize the nonapeptide bradykinin within 8 days and was used to synthesize the octapeptide angiotensin II in 1965. It has since become the standard method for peptide synthesis, in particular if the alternative of bacterial expression is less favorable.

2. The competitive race of three teams of chemists for the synthesis of insulin, which was successful for the team of Helmut Zahn at RWTH Aachen in 1963.

My work in the new Chemical Lab of Bayer began in September 1967. I joined several groups of chemists, pharmacologists, etc. involved in different discovery programs for interesting small molecules of potential use as drugs for different diseases. One of the programs was targeting molecules reducing the adhesion of blood platelets. A large number of molecules were synthesized and screened for activity in a series of in-vitro and in-vivo models comprising blood platelets and other targets. Researchers were encouraged to provide input in terms of drug candidates into the priority programs, as well as to spend some time on areas of their own imagination and fantasy. My work led to a variety of fatty acid derivates and it turned out that linolic acid derivatives showed promise to be further investigated in human studies. The ethyl ester was chosen as a candidate for a Phase I study in healthy volunteers and a liquid emulsion was prepared by Pharmaceutical Technology. From the regulatory point of view, no special requirements were applicable in Germany at the time: Formal guidelines concerning pharmacotoxicological studies required in the development of drugs before clinical studies and registration were only introduced in 1971 and furthermore linolic acid was regarded as a general

component of human food and the corresponding ethyl ester could be regarded as comparable to the glycerol ester which is the prevailing type of molecule in fatty food.

The study was prepared, but it wasn't carried out. Management had realized that aspirin (ASA), first synthesized in exactly the same company in the year 1888 and found some years before to reduce the aggregation of blood platelets, would be superior to any new drug still to be developed for this indication. There was little to argue against, and the research program was terminated.

I continued my work in the other areas relevant at the time. My extra interest outside of the re-search programs was in new synthetic methods like electro-chemistry and photo-chemistry. Nothing spectacular resulted from these excursions into new methods and from regular re-search work on new active drug candidates.

New Horizons.

In the end of 1970, I was asked whether I would be interested in joining the tiny emerging group of project management being introduced at the time. It had started with the design of a carefully structured development network plan with a few organizational adjustments regarded as appropriate to develop new drug candidates from preclinical to clinical Phases I, IIA, IIB, III, regulatory submission, approval and launch. This structuring of drug development had taken place in parallel to the late stages of development of the New Drug Law in Germany that was finalized in 1974. On the EU level, comparable work had resulted in a 1965 guideline out-lining the essentials of prerequisites (safety, efficacy and quality) for the approval of new drugs replacing mere registration without substantial review.

I agreed to joining this group led by a charismatic boss. In January 1971, I started working on a few new projects in different stages of preclinical or clinical development. Any involvement in project team meetings and regulatory support required for these projects (e.g., INDs and other clinical trials permissions, as well as master dossiers for regulatory submissions) was to be provided by this small group. We also had to provide status reports, keep the network plans (partly with the help of mainframe computers that turned out to be of questionable benefit) and project data files up-to-date, prepare decisions, organize supplies, follow up due dates and chair project team meetings. It turned out that certain countries, mostly those involved in early clinical development or complementary CMC work (like Japan), did require additional support and communication. Following Phase I, the project team chair moved to a representative of the Medical Department.

Marketed products were mainly handled by project teams chaired by marketing managers and in case of regulatory support needed (e.g., change management and labeling), the Regulatory Affairs Department was in charge, a group that formed the complementary part of the Project Management unit within Development.

Important projects in clinical development at the time were nifedipine and clotrimazole. The latter had been a promising candidate for the treatment of systemic fungal infections before I joined Bayer in 1967. It turned out, however, that the efficacy of the compound was fading away due to significant enzyme induction during oral administration. Consequently, the focus of development moved to formulations for topical use, i.e., cream, dermal solutions and vaginal tablets.

Clinical trials with clotrimazole were carried out in a few countries, in particular in Germany, Japan, the

US and selected countries with dermal infections not so common in moderate cli-mates. The US was a very special case since Bayer was a nobody there. The company had lost its assets including the Bayer Cross and trademarks during the first World War and they could be reclaimed only in 1994. Bayer Aspirin was the property of Sterling Drug/Sterling Winthrop. During that entire time span, Bayer was cautious not to use any of its broadly used trademarks “Bayxyz” in the US in order to avoid legal conflicts. Furthermore, it turned out that several at-tempts to develop new drugs in the US failed before the development of clotrimazole (by the Bayer/Schering (Plough) joint venture Delbay), which was approved in the US in March 1975.

The FDA boasted about the short review time of just 9 months, while the average for NMEs at the time was 36 months. The launch (TM Lotrimin) of the cream was slightly delayed because spermaceti (a product from a protected species) had been used and this required re-formulation (all countries) with an artificial excipient of comparable properties.

The regulatory review process in Germany was far more time consuming. Due to interferences with the lengthy emerging of the new drug law, it took almost 30 months before solution and cream were approved in August 1973. Nevertheless, the launch in November 1973 was perceived as a time mark for a new era of a new product.

The development of nifedipine was far more complicated and time-consuming than clotrimazole. The API, a light-sensitive compound formulated with PEG in a soft-gelatin capsule, was the first dihydropyridine in development and it required some perseverance (initially by the inventors) to overcome the initial resistance and disinterest. The indication to be pursued was angina pectoris, not hypertension. Investigations in the mechanism of action led to the under-standing of calcium channel blockers, which took a while. Nifedipine was Bayer’s main asset within a broad research/development collaboration with the French company Rhône-Poulenc. Despite a positive spirit within that cooperation, things got more difficult when projects advanced closer to the market and each partner thought that its candidates in the pipeline were more valuable than the other partners’ products. Rhône-Poulenc gave up its interest in nifedipine at some time.

My first contribution to the nifedipine capsule project was the US IND. That went quite smoothly, but the following steps in clinical development were more difficult. The US organization did not make much progress in clinical development and we were told that physicians involved did not understand the mode of action and were more interested in beta-blockers. It took a while before the project was offered for license to a major Swiss company. This attempt failed after some time and the project was offered to Pfizer. They carried out some complementary studies and got the drug approved in the end 1981, after 21 months of FDA review. Bayer had retained the right to launch this drug 4 years later.

The most important/successful countries for nifedipine after launch in the second part of the ‘70s were Japan and Germany. Japan used to be a country with certain complementary requirements: repetition of some toxicological studies, as well as CMC/stability studies and clinical development in Japan. The acronym most often heard in this context in the pharmaceutical industry was NTB (non-tariff trade barriers), the mix of requirements designed by Japanese authorities reportedly to keep the foreign competition down. Germany was also complaining about the Japanese import restrictions concerning import of German cars. In 1984, the US started “market-oriented/sector selective (MOSS)” talks in order to overcome the obstacles in four areas, including pharmaceuticals. Success was moderate, but the subsequent International Conference on Harmonisation (ICH) brought significant changes—almost unexpected by critical observers—in drug development in all territories involved. I recall one of the last

ICH meetings at San Diego, which began just after election day in November 2000. Even a member of Bayer's Chinese subsidiary attended. At the time, the contribution to global drug development of the Bayer organization in China was next to nothing. A good reason to reconsider the changes in the last 20+ years.

Nifedipine (Adalat) became a very successful drug. Additional formulations were developed (e.g., a slow release tablet for b.i.d. administration and the once daily formulation of GITS/OROS are still being used as effective and well tolerated treatment of hypertension in a broad range of patients). It is of interest to note that nifedipine drug substance and its methods of manufacture have never been subject to patent protection. This sheds some light on the perception of priority of the drug in the early research stages within the company. The first patents were granted for the soft gelatin capsule and subsequent slow release tablet formulations. I re-call being cross-examined on behalf of Pfizer to defend against claims by a generic company against the soft gelatin patent in 1988 (NYC), which was quite successful.

Since Bayer had a significant line of antiinfectives at the time, mainly penicillins, the two Acyl-ureido-penicillins Mezlocillin and Azlocillin that made it to the markets may be of interest. Both penicillins were broad spectrum, but azlocillin was particularly effective against Pseudomonas. The development in Germany started in 1972/1973 and, unlike earlier projects, they were approved early in 1977 in a fairly short time span of four months; azlocillin even with less than 100 patients. Regulators did like the narrow focus in case of azlocillin. The Dutch Head of Health Authority, who had delayed the approval of nifedipine repeatedly, did encourage the submission and approval of azlocillin. Development in the US was more time-consuming be-cause colleagues in clinical development were hesitant due to the uncertain commercial success and the overlapping process of merging with Miles Laboratories. This changed when the right person came onboard, rolled up his sleeves and started working. The commercial success following approval in 1981 has probably not been outstanding, but the team of colleagues involved in the clinical development had consolidated and gained a lot of experience and cohesion for the next anti-infective: ciprofloxacin.

Ciprofloxacin: The first meeting was called end of October 1981 and it was a priority project right from the beginning. We were ambitious to proceed to Phase I within the shortest possible time span. This required synthesis of the API and the definition of the form to be developed (salts or betain) was still open. I found that the Japanese development of Ofloxacin underway at the same time was using betain (not any water soluble salt) and I found this was a missed opportunity with regard to the simultaneous development of an injectable. It was found that ciprofloxacin hydrochloride monohydrate had adequate properties suitable for the development of tablets and injectable. First priority was assigned to the development of the oral administration and some helpful findings contributed to keeping marketing wishes at a level compatible with the initial setting of priorities: an aqueous solution for oral administration was so bitter that the idea soon disappeared, and an injectable solution for IM administration of 2.5 % was problematic in terms of local tolerance. The initial idea of a 1% solution for IV infusion or injection was soon given up, due to some cloudy solid material appearing in the vials. It was decided to abandon the hydrochloride and to switch to the lactate at a lower concentration, which was made from the betain (code q 3939) and lactic acid.

Following two 4-week studies in rats and dogs, we could proceed to clinical Phase I in May 1982, more or less 6 months after the start. This was possible in Germany since the regulatory requirement at the time was to deposit the nonclinical safety studies (toxicology and pharmacology) and Health insurance details with the Health Authority. No information on study parameters, protocol or CMC was required. The first study compared tolerance and PK of a capsule containing the API and an aqueous oral solution

(a somewhat brave part of the study due to the bitter taste). Bioequivalence was shown.

It was common at the time to expand clinical development in more countries when Phase I study results were promising and resources in clinical development could be established. The fact of having jointly developed two penicillins not too long ago was helpful for fast implementation. The development of a Project Target Profile outlining location and bacterial strains responsible for the infections became an important tool in the coordination of targets. Given the daily doses, drug supply became a challenge but never caused a delay in progress. In most countries, the time span between oral development (Tablet) and Injectable was approximately 1.5 years and grew, as in the US, to 3 years with regard to the launch. Ultimately, the injectable was approved there on the basis of bioequivalence.

Regulatory submissions in Germany for tablets and injectable were made in October 1985. At the time the German Health Authority (BGA) was flooded with thousands of submissions referring to the mostly unknown original submissions, a procedure scheduled to end soon after the implementation of a drug amendment. We tried to overcome this blockade and were told that a priority review had been established, due to the efficacy of ciprofloxacin and the fact of hav-ing both the tablet and the injectable solution.

Bayer has undertaken more efforts to develop line extensions of ciprofloxacin which turned out to be quite time-consuming: Cipro oral suspension and Cipro OD. Furthermore, a variety of NMEs were taken into development and one of them, Moxifloxacin, with an increased efficacy against gram-positive and intracellular strains, was launched end of the century. In the mean-time, many earlier chinolones have disappeared and the remaining ones are subject to regulations to ensure that the potential benefit outweighs the risk of their use. Ciprofloxacin and Moxifloxacin which have much contributed to Bayer's success, are still available.

Following my years at Bayer, I was invited to support a start-up project for T1D that was seek-ing advice from Health Authorities in the EU EMA and the US FDA. This project could not be continued after 2006. I was, however, invited to join Dr. Alexander Fleming and his Kinexum team to start an anti-tumor project in Hong Kong and China, and to transfer and convert it into a successful IND in the US. The molecule was a pegylated protein. The issue on the CMC side was that the pegylation pattern of earlier and later protein batches were not really identical and the client had to repeat synthesis/purification of the recombinant protein and its PEG version, as well as repeating some toxicology studies.

This was the first of a long list of projects which followed, including small molecules, peptides, recombinant proteins and broad variety of projects and combinations of very different sources. This work on various scientific topics was always fascinating to me and brought together different people from different races, cultures, colors and religions, and I regard this as a main ingredient of a peaceful world and the enrichment of my life.
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