Healthcare industry BW

Exalon GmbH – preparation of regulatory submission packages

Exalon GmbH, based in Radolfzell, Germany has two key principles that account for its success: always keep in contact with the public authorities and always know the right doors to knock on. The company, run as a team of three, Dr. Michael Braun, Sibylle Teuchmann and Michael Zingrebe, has been supporting life sciences companies and service providers in the electronic submission of applications for obtaining marketing authorisation for medicinal products and the electronic reporting of modifications to approved medicinal products since 2007. The three experts told BIOPRO about the lack of uniformity in such procedures despite the growing acceptance of paperless submission of application dossiers.

Ms. Teuchmann (ST), why are the health authorities increasingly requesting regulatory submissions to be submitted electronically?

ST: The regulatory requirements needed to obtain marketing authorisation for a medicinal product are becoming more and more complex. This is particularly true for the requirements for clinical and preclinical testing where constant progress is being made and new insights gained as well as changes in drug quality occurring. As a consequence, the volume of data and the complexity of the regulatory submission packages have grown, which in turn has made the processing and assessment of paper applications more and more difficult. Electronic applications and submissions have considerable advantages over paper versions.

Mr. Zingrebe (MZ), what are the advantages of electronic submissions?

MZ: Electronic submissions considerably reduce the time required to process and assess up to several hundreds of A4 folders - the electronic file fits on several CDs at most. An electronic dossier can be processed, assessed and dealt with centrally, which means that experts such as toxicologists, pharmacists and medical experts are able to access the data simultaneously. In addition, it takes just seconds for the reviewers to navigate between huge amounts of data rather than having to deal with several shelves of A4 folders. Electronic data submission also allows the retrieval of information using full-text search options. The introduction of an international standard for the transfer of regulatory information from the pharmaceutical industry to the regulatory agencies, the eCTD (electronic Common Technical Document), led to the introduction of the "eCTD lifecycle". This enables the applicants to submit and indicate changes from the previously submitted version in the form of a new eCTD sequence. As a result, both the regulatory authorities and the applicants will always have an up-to-date approval dossier. This is not possible when working with paper versions.

How big are the dossiers on average?

Sibylle Teuchmann
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ST: In the EU, the submission packages often consist of several hundred documents with a total of 100,000 to 200,000 pages. In the USA, the dossiers are even bigger and can consist of several thousand documents. I do not know whether there is a limit to the maximum number of documents that can be submitted.

Dr. Braun, how do you keep up-to-date with new regulations and specifications?

MB: We rely on documents published by the regulatory authorities and up-to-date literature, newsletters and information published by associations. It is a good idea to contact the relevant authorities prior to submitting an application in order to discuss certain aspects. Regular participation in congresses and workshops is another obligation.

Can you tell me more about the internationally valid eCTD format?

MB: As regards content, the eCTD is based on the same format as the CTD (Common Technical Document), which consists of 5 modules. Module 1 contains administrative information and national

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information as well as drug product information. Module 2 contains common technical document summaries (production and quality, preclinic and clinic). Comprehensive information about the production and quality of a drug is in Module 3, the preclinical and clinical study reports (e.g., research reports and literature) are in Modules 4 and 5. The eCTD references and identifies the individual documents in a simple electronic table of contents; a full table of contents can be quite large. In addition, the table of contents also contains information about the approval dossier and the eCTD lifecycle in the form of metadata. The individual electronic documents also have their own internal navigation functions.

What are the latest developments relating to the eCTD?

MZ: The eCTD standard is constantly expanding and being adapted. For example, on 1 January 2009, the specifications concerning the administrative information in Module 1 have changed in the EU; new data and documents have been included. From January 2010, eCTD will be mandatory in the EU. Some regulatory authorities have been using eCTD for quite some time, these include the American FDA and the European drug agency EMEA. Broader acceptance and growing experience have led to stricter validation criteria. Applicants have to comply with the specifications far more closely than they did a few years ago. In addition, efforts are ongoing to develop methods that can transfer the content of some documents into formats such as XML that are easier to process.

What is a successful strategy for the preparation of dossiers for obtaining marketing authorisation of drugs?

ST: When preparing individual documents, I find it important to keep in mind the later use of these documents in an eCTD. This means that formal criteria should be followed, for example the documents should be formatted according to eCTD specifications. Both staff training and the use of style sheets are recommended. It is also advisable to prepare and maintain a project plan well before submitting the documents. This project plan provides information about the type, extent and availability of the individual documents. The plan also needs to be discussed with the department in charge of application submission. In individual cases and complex dossiers, it is further recommended to contact the regulatory authority and discuss specific questions that might arise. This can be done in so-called "presubmission meetings" where an initial rough draft of the dossier can be presented. It goes without saying that the applicants need to have thorough knowledge of the valid specifications, guidelines and regulatory requirements.

What is the time frame for preparing a submission package and how is this done?

ST: A comprehensive dossier might take three to four months to compile. The documents required for a marketing authorisation to be granted are prepared hand in hand with the entire drug development process. Work on the dossier starts with the definition of the table of contents according to the regulatory specifications. The dossier will then be prepared step by step following a project plan. The documents are formatted in parallel with the processes being controlled. Finally, the documents will be hyperlinked. In this last phase, applicants have to be aware that "last minute" changes might be necessary and may need to be incorporated into the application. Technical validation of the dossier and quality control conclude the preparation of the dossier.

What do you think are the challenges for smaller companies, i.e. biotech companies, in preparing electronic submission packages?

MB: For small pharmaceutical companies or biotech companies who are applying for the marketing authorisation of products, the time and effort required to prepare an electronic submission package is, in relation to the size of the companies, immense, because the formal requirements are the same for big and small companies. Biotech companies who depend on investors and have a small but highly specialised product portfolio, usually only apply for the marketing authorisation of a few products, if they have not outlicensed their substances prior to the authorisation process. Due to tighter budgets, smaller companies have to make precise calculations and decide whether it is worthwhile for them to establish an in-house infrastructure for the preparation of electronic submission packages or whether it would be cheaper to set up partnerships with other pharmaceutical companies.

Do you often have to react to abrupt regulatory changes?

Michael Zingrebe
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MB: Modifications to international standards are usually known about well in advance. A slightly bigger problem is the requirements of national regulatory authorities that are published at short notice. This is a particular problem because national requirements might differ considerably in individual specifications. There are big differences between submission packages for European and American regulatory agencies. When submitting an EU and US application concurrently, there is a lot of extra work. Some countries have special regulations that differ slightly from the eCTD specifications. The use of the eCTD lifecycle is also not 100% standardised in the different countries. Taken together, such particularities make the preparation of submission packages quite difficult. Depending on where applicants get their information from, it may be more or less contradictory. Therefore, it is important to be in direct contact with the regulatory authority and know the people to contact should the need arise.

What is so special about Exalon's philosophy and what are your future goals?

ST: Many years of cost-intensive research and development are devoted to just one objective, namely obtaining marketing authorisation for new medicinal products for the more effective treatment of patients. With our background and experience, we can prepare the results of this type of research in

a way that enables the authorities to quickly find the necessary information and links and be able to come to a well informed decision in a relatively short time. This means that we will, if required, make the impossible possible, particularly in cases where tight deadlines for the submission of dossiers have to be met. In the end, our common goal is to provide patients across the world with quick access to more effective, safe, new therapies.

MB: We work with professional experts such as medical specialists, pharmacists and toxicologists whose expertise complements our specialised services well - for example they prepare clinical and preclinical study documents for us. We have plans to expand this network in the future.

Background:

Dr. Michael Braun studied biology at the University of Saarbrücken and received his PhD from the University of Tübingen. During his studies, he also trained in IT systems administration and PC application consulting. Subsequently, he worked for four years as regulatory affairs manager for an international pharmaceutical company. Dr. Michael Braun is a member of the German Society for Drug Regulatory Affairs (DGRA) and the Regulatory Affairs Professionals Society (RAPS).

Sibylle Teuchmann spent four years as medical information specialist working for the WHO Institute in Lyon, France. In 1996, she began working in the pharmaceutical industry where she specialised in electronic submission and document management. Prior to the foundation of Exalon, Sibylle Teuchmann was the head of the "Regulatory Operation" department of an international pharmaceutical company for five years. She is a member of the Organisation of Professionals in Regulatory Affairs (TOPRA), the Regulatory Affairs Professionals Society (RAPS) and the Drug Information Association (DIA).

Michael Zingrebe studied "bioscientific documentation" at the Hanover University of Applied Sciences before spending three years at the Tumour Centre of the Hanover Medical School. Prior to founding Exalon, he spent nine years as a specialist for information and document management systems in the "Regulatory Affairs" department of a globally acting research-based pharmaceutical company where he made considerable contributions to the introduction of eCTD processes and systems.

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