Preparing a drug registration for the US and the EU: Parallel or sequential applications? – Part 1

Authors
Nathalie Boeglin, Director; Alice Rolland, Regulatory Scientist; Frederic Pailloux, Senior Director; David Uguen, Executive Director; Voisin Consulting Life Sciences.

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Abstract
Pharmaceutical companies (also referred to as ‘sponsors’ or ‘applicants’) involved in global drug development usually aim to submit marketing authorisation applications to both the US FDA and the European Medicines Agency (EMA). The ability to file the same information to both the FDA and the EMA with little or no delay between the two applications has been significantly improved by the International Conference on Harmonisation (ICH) process and the development of the Common Technical Document (CTD) format which can now be used equally in the two regions.

Sponsors are usually aware of the cultural and medical differences that exist between the two regions, particularly in terms of disease management. Sponsors also need to take into consideration that the FDA and the EMA use different assessment approaches, with different legal requirements, which substantially impact the content of the application for product registration in the US and the EU.

Due to obvious time and budget constraints, applicants are now considering the preparation of one global regulatory strategy and ideally one single core application which needs minimal adaptation to meet both US and EU requirements. To do so, sponsors may adopt the “parallel approach”, where one core dossier is developed and geographical/regional considerations are included and highlighted during preparation of the dossier to allow the simultaneous completion and submission of the applications in both regions. They may alternatively choose the “sequential approach”, where the application is prepared for the first region of interest (and submitted in that region first) and then adapted/converted to meet the requirements of the other region (and submitted there subsequently).

This two-part paper provides an overview of the main challenges faced by applicants for the conversion of one dossier from one region to another, and highlights the potential differences in the content of the CTD between the two regions. It also aims to help sponsors decide between a sequential and a parallel preparation. Part 1 of this paper focuses on the Quality/CMC (chemistry, manufacturing, and controls) sections, while Part 2 will cover safety/nonclinical, efficacy/clinical and Module 1 – administrative information.

Introduction
Submitting a new drug application (NDA) or a biologic license application (BLA) in the US or a marketing authorisation application (MAA) in the EU is the ultimate goal of all sponsors and a mandatory step for the commercialisation of any medicinal products. As applicants plan to put their product out in both markets, they have to consider a global regulatory strategy including a product development plan and regulatory milestones for registration in the US and the EU.

The regulatory strategy should include decision-making criteria and planning for parallel or sequential preparation and submission of the MAAs. Both are possible, as the Common Technical Document (CTD) format, which is used for the presentation of the data, is common – for the most part – to both regions. The CTD content is driven by ICH guidelines for Quality (Q, also known as CMC in the US), Efficacy (E, clinical) and Safety (S, nonclinical), and is almost equally applicable in the US and the EU.

If planned adequately, these two applications can be prepared and submitted nearly simultaneously. With the parallel approach, one core dossier is targeted and geographical/regional considerations are included and highlighted during preparation of the dossier to allow the simultaneous completion and submission of the applications in both regions. Ensuring a successful parallel preparation of MAAs for the US and EU requires the allocation of extensive resources and strong project management to ensure and maintain coordination. In this approach, customisation of the dossiers to address US and EU specificities is completed at the very end of the preparation process.

Alternatively, the drug registration applications can be prepared sequentially (typically starting with the application in the geography where the company’s headquarters are located). Sponsors based in the US will typically prepare and submit their NDA (or BLA) focusing first on addressing the FDA’s requirements. Following submission of the NDA (or BLA), the sponsor will then manage the conversion of the US file into the MAA for submission to the European Medicines Agency (EMA) (or to any European national regulatory authorities, depending on the selected registration pathway).

It is important to keep in mind that cultural and medical differences, which translate into different therapeutic guidelines, exist between the two regions. Also, differences in the assessment approaches and legal requirements between the EU and US may impact substantially the content of the applications for medicinal product registration. In the EU, multiple competent authorities, including the EMA and its varying scientific committees, can be involved throughout development. During clinical development, national authorities and other committees (eg, ethics committees) can take part in the evaluation of clinical trial applications (CTAs). In addition, MAA assessments are performed by different member states in Europe, with potentially different medical practices in diseases management. In the US, the review process is more integrated. The same “Review Division” of the FDA is involved in the product from early development through approval of the NDA (for a synthetic drug) or BLA (for a biologic drug). These factors lead
to different review processes between the two regions, with the well-known “top-down” approach in the EU and the “bottom-up” approach in the US, resulting in different expectations in terms of content and level of detail.

This paper attempts to clarify the nature of these differences between the two regions, and to suggest (best?) practices for the conversion of an NDA (or BLA) into an MAA. In this article we first consider in details the technical sections related to CMC/Quality (Modules 2.3 – Quality Overall Summary and Module 3).

Quality/CMC

Thanks to ICH guidelines, requirements in terms of Quality documentation (also referred to as CMC [Chemistry, Manufacturing, and Controls]) can be considered as “globally similar” when one compares what needs to be provided in a drug registration application in the US (as per the Code of Federal Regulations (CFR) Title 1 Section 14.50(d)(1) [21 FR 314,50(d)(1)]) and the EU legislation, as defined in the Notice To Applicants, Human, Volume 2. However, the FDA and EMA actually have different requirements, notably in the level of detail to be provided in each section of the application. As previously discussed, the FDA often requires more detailed data while the EMA requires condensed data, leading to the need to summarise several sections when converting an NDA/BLA into an MAA.

Of note, a Qualified Person (QP) is mandatory in the EU to release the batches of drug product for sale and to certify that they are in accordance with the relevant requirements (good manufacturing practice (GMP) compliance). The EU QP must have specific qualifications and be located in one EU country. In the US, there is no such QP requirement and it is left to the company to define a competent person responsible for compliance with FDA regulations.

Table 1 provides an overview of some points for consideration in converting the quality/CMC sections of an NDA/BLA into an MAA.

### Table 1: Points to consider when converting the Quality/CMC section of an NDA/BLA into an MAA.

#### Module 2.3 Quality Overall Summary (QOS)

While cross-references to Module 3 are not limited in the NDA/BLA, it is recommended for the EU to write the QOS as a stand-alone critical summary document and to limit cross-references. This allows all important information to be summarised within Module 2.3.

#### Modules 3.2.S Drug Substance (DS) and 3.2.P Drug Product (DP)

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| General | Drug master files (DMFs):  
- US: Cross-reference to a DMF for chemical or biological active substances, excipients, raw materials and/or container closure system(s) is possible.  
- EU: The DMF (or active substance master file (ASMF)) applies only to active substances of non-biological origin.  
For complex biologically active raw materials used in the production of cell and gene therapy, reference to the DMF is allowed in the US but not in the EU, creating important issues around intellectual property between suppliers and users of those raw materials.  
Note: The European Directorate for the Quality of Medicines (EDQM) is currently working on the standardisation of raw materials used in the production of cell and gene therapy products.  
In the EU, the demarcation between the starting material, drug substance (DS) and drug product (DP) is critical, particularly for cell and gene therapies in accordance with the European Regulation on advanced therapy medicinal products (ATMPs).  
- “The active substance shall be composed of the engineered cells”.  
- “The finished medicinal product shall consist of the active substance formulated in its immediate container for the intended medical use”.  
This demarcation is not always the same in the US and often requires significant reorganisation of Module 3 for MAA preparation.  
More GMP-related information (deviations, out-of-specification results, etc) is often provided within the NDA/BLA in the US, while such information is part of the Quality System in the EU to limit the risk of repeated and frequent variations when changes occur.  
3.2.S.2 | DS development sections are more detailed in the US NDA/BLA than in the EU MAA.  
3.2.S.4 | European Pharmacopeia (Ph Eur) versus US Pharmacopeia (USP) DS control methods:  
- Ph Eur sometimes requires more restrictive specifications limits than USP.  
- Available Ph Eur monographs should be used as reference for the EU MAA.  
- The FDA may accept Ph Eur as reference if more restrictive than USP.  
3.2.P.2.2 & 3.2.P.2.3 | The Pharmaceutical Development section is usually not as developed in the NDA/BLA compared with the MAA. However, the NDA/BLA may be more detailed, especially for submissions including a prevalent quality-by-design (QbD) approach where the FDA prefers to have a complete Pharmaceutical Development section.  
3.2.S.4, 3.2.P.4 & 3.2.P.5 | Control methods are usually more detailed in the NDA/BLA than in the MAA. They are based on the manufacturer’s standard operating procedures (SOPs). Complete SOPs may be included in US NDA/BLA Module 3.  
3.2.P.4.3 | On review, the FDA may request full analytical methods validation reports for some methods deemed critical, more often than in the EU.  

Regulatory strategy
Table 1: Points to consider when converting the Quality/Clinical aspect section of an NDA/BLA into an MAA (cont’d).

3.2.P 5.5 Both the US and EU are sensitive to potentially genotoxic impurities, but the EU has stricter requirements for the methods used for the identification and qualification of impurities.

Module 3.2.A Appendix

3.2.A.2 For viral adventitious agents, viral safety evaluations are required in both regions, but EMA requires more detailed information on the methods used.

Module 3.2.R Regional Information

In the EU, the following information should be provided:
- The Process Validation Scheme for the DP, which is used to provide evidence that the processes are able to consistently produce a finished product of the required quality.
- If applicable, information related to medical devices included in the packaging of the DP, eg, CE-marking information.
- When applicable, Certificates of Suitability (CEPs) delivered by the EDQM can be provided to show that the quality of the substance is controlled following the Ph Eur monograph (with additional tests, if necessary), and that the substance complies with the EU requirements on minimising the transmissible spongiform encephalopathy (TSE) risks.
- If the medicinal product contains or uses in the manufacturing process materials of animal and/or human origin, information showing compliance to Directive 2001/83/EC is mandatory.

In the US, the following information should be provided:
- Executed batch records should be submitted in Section R.1.P (Executed Production Records) for the batches produced in support of the NDA/BLA.
- Comparability protocols describing the specific tests, studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of post-approval manufacturing changes on the identity, strength, quality, purity, and potency of the drug product as these factors may relate to the safety and effectiveness of the drug product. Comparability protocols are optional. If a comparability protocol is proposed, it should be included in Section R.2.P (Comparability Protocols). Approval of a comparability protocol can justify a reduced reporting category for the particular post-approval change.
- Package validation method(s). It is only possible to describe validation methods in relevant Sections 3.2.S and 3.2.P. For some products, the validation methods can include FDA laboratory analysis to demonstrate that an analytical procedure is reproducible by laboratory testing. A complete package validation method must then be submitted in the application (21 CFR 314.50(e)(2)(i) and 314.94(a)(10)) and should be included in Section R.3.P (Methods Validation Package).

Discussion

The purpose of this paper is not to provide an exhaustive list of differences in the Module 3 between the two regions, but to point out the critical items for consideration when converting an NDA/BLA into an MAA and vice versa.

As far as the Quality documentation of the drug registration applications is concerned, the main differences between the US and the EU regions are directly linked to the different levels of detail generally required for each section of the application due to the different review processes in the two regions.

Of note, the Quality documentation is compiled from early stages of the clinical development as the CTD format also applies to the investigational medicinal product dossier (IMPD) of the EU CTAs and to the Module 3 of the US IND applications. Thus sponsors undertaking a global drug development programme would generally favour the parallel approach for the preparation of the Quality Modules of the CTD for registration applications, given that they have to prepare the Quality sections of IMPD and IND at the same time for the two regions.

Part 2 of this paper will focus on points for consideration for the other technical sections of the CTD, ie, safety/non clinical, efficacy/clinical and Module 1 – administrative information, and will discuss the pros and cons of parallel vs sequential preparation of the CTD as a whole.

References

2 21 CFR 314.50: Code of Federal Regulations, Title 21, (Revised as of 1 April 2013).