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WHITEPAPER

DIFFERING CMC REQUIREMENTS: US AND EU

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Torsten joined PharmaLex in 2015 as a Senior Manager in Regulatory Affairs. Using his 15+ years of experience in CMC authoring in Europe and the US, he has been consulting our clients in the regulatory specifics of these regions. In his function as International CMC Service Coordinator he ensures the best support for our customers from our global network of international experts. His longstanding experience in life-cycle management and GMP expertise allows him to advise clients in all quality related regulatory maintenance activities.

Specialties: Global CMC requirements, life-cycle management, systems, procedures and workflows

Introduction

Over the course of the past years, companies' economic interests have spread across the globe, with the pharmaceutical industry not being an exception. As pharmaceutical products are highly regulated, the different regulatory requirements in various regions impose obstacles when considering expansion into other markets.

These difficulties have sometimes prevented new drugs from reaching patients in need. Therefore inter-regional co-operations were begun to harmonize international coordination, foremost being the International Council of Harmonisation (ICH). Since its inception, the ICH has published many harmonized guidelines concerning all aspects of medicinal products, their manufacturing, control and distribution.

In the United States and Europe most ICH guidelines have been incorporated into the respective regional regulations. Focusing on the part describing product quality of drug applications – Modules 2 and 3 – this article will examine the differences between these two regions.

The format in which the content is presented in new drug applications is regulated by ICH guideline M4. It is known as the Common Technical Document (CTD) and the application is provided electronically as eCTD to the respective evaluating health authority. While the eCTD/CTD format has been established in ICH M4, it was also incorporated in the US as Guidance for Industry and Notice to Applicants in Europe.

While the defining guidelines are the same in these two regions, the practical incorporation and interpretation show significant differences which originate from the varying circumstances and mindsets at the respective authorities.

"...different regulatory requirements in various regions impose obstacles when considering expansion into other markets"

The Food and Drug Administration (FDA) in the US is a single body, responsible for food, drugs (including medical devices) and cosmetics regulation (covered in the FD&C Act). The European Medicines Agency (EMA) in Europe only regulates medicinal products (drugs) that qualify for centralized procedures and all regulations in Europe need to be coordinated between the member states. Medical devices are regulated completely decentralized and therefore not uniformly.

Additionally to the different settings of FDA and health authorities in Europe, the relationship between industry and the regulatory agency is largely different in both regions. In Europe the pharmaceutical industry approaches the health authorities with trust, with the expectation that the applicant will point out critical aspects and present appropriate selective data. In the US the FDA approaches the industry from a more demanding position, requiring raw data and GMP documents, examining every aspect of each application in great depth.

When comparing CMC dossier requirements for both regions, it is essential to bear these contrasts in mind to understand the differing requirements.

General differences

Both regions have unique procedures which are unparalleled in other regions and still not harmonized. A few examples are described below.

Drug Master File in the US: The DMF procedure in the US features several types of DMFs including active substances, colorants, flavors, excipients, facilities, operating procedures, packaging materials, intermediates, raw materials and other fixed combinations of information.

In Europe only the Active Substance Master File (ASMF, formerly known as DMF) procedure is utilized, which differs vastly from its US counterpart.

Certificates of Suitability to the monographs of the European Pharmacopoeia (CEP) are the result of a certification process in Europe which confirms compliance of a drug substance to the requirements of the respective monograph in the European Pharmacopoeia (EP). CEPs can be used instead of an ASMF during drug product application filing. CEPs are not accepted in the US.

The United States Pharmacopoeia (USP), unlike the EP, already features many finished product monographs and therefore drugs need to comply to these if a monograph is available.

FDA performs product specific inspections during the approval procedures while European health authorities rely on site specific inspections for the product type (sterile, solid, etc.). This has a significant impact on timelines and potential risks for a new submission.

GMP documents are required in US filings while in Europe these documents are explicitly requested to be excluded, as the GMP life-cycle would trigger regulatory variations without content changes.

Overview of main differences

As aforementioned, the mindset and focus of the respective health authority is a determining factor of the expected data and its presentation. But also tradition and legislation already in place before the harmonization processes began also play a big role in the Agency expectations. There are some historically grown differences which greatly influence the presentation, anticipated content and terminology of the application dossier.

While the FDA assessors expect an amplitude of data (as unfiltered as possible) to evaluate and draw a complete picture, the European assessors expect an application which guides the evaluator through the critical aspects of the product. Therefore an application to the FDA is more data driven and a submission in Europe contains large portions of narrative, selects the data to be provided and abstracts information from GMP sources rather than presenting them directly.

In the following table some of these differences are specifically highlighted:

US	EUROPE
The Quality Overall Summary is a mere summary without evaluating comments. For NDA filings the QOS is provided in CTD format. Generic ANDA filings use a specific Question-based-Review (QbR) format. The assessment of the application is mainly performed on the data and reports presented in Modules 3 to 5. In case of ANDA assessment the QbR is utilized in a similar fashion as the QOS in Europe. However only the quality summary is provided in QbR format.	The QOS is an evaluating summary by a pharmaceutical expert within the industry. QOS is always provided in CTD format and seen as a main tool for the assessment of the application file. It is being utilized by clinical, non-clinical and quality assessors to gain a critical insight into the content of the application. Modules 3 to 5 are mostly consulted when additional detail is needed.
Manufacturing: Executed batch records presented in module 3 (regional information), 3.2.P.3 includes reference to GMP documents or the GMP instructions itself.	Manufacturing: no batch records to be included in module 3 (whether executed or blank), 3.2.P.3 should not include reference to GMP documents, but abstract information of these.
Process validation on 1 batch sufficient, however, only validated machinery and batch sizes are approved for manufacture. If no validation available at filing, a Validation Commitment is sufficient.	Process validation of 3 batches expected. Validation required on type of machinery and appropriate material ranges need to be validated. If no validation is presented, a detailed validation scheme in 3.2.R. is expected.
In alignment with USP, the defined specifications are usually understood as end of shelf-life limits. Therefore assay specifications of 90% - 110% are the norm.	Specified limits for release and end of shelf-life are separated. The term "specifications" usually refers to the release specifications. Standard assay limit is 95% - 105%, deviating shelf-life limits need to be justified.
Identification: 1 test sufficient. Test for water content is routinely required	Identification: 2 tests with 2 different detection principles required. Disintegration and color identification testing required.
Methods: Usually in-house SOPs with detailed working instructions and material. System suitability test and compliance with USP (if applicable) should be mentioned.	Methods: summaries with general instructions and abstracted preparations (solution ratios rather than exact weigh-ins). Focus on calculations and chromatographic conditions.
Stability: Required amount of batches and storage time for dossier depend on dosage form and stability of product. As little as 1 batch with 3 month (ANDA of stable product) data required.	Stability requirements in alignment with ICH guidelines. Dossier requirements do not vary.

By design, the CTD structure contains a designated section for regionally relevant data – Regional Information. The content of this section is unique for each region.
The table below provides an overview of the regional information of both the US and Europe;

REGIONAL INFORMATION	
USA	**EUROPE**
Method Validation Package: Detailed information on materials and methods (including internal SOP numbers, batch information, safety data sheets, etc.) presented in module 3 needs to be provided in Module 3.	Certificates of Suitability: If CEP available, the signed certificate should be presented here. All CEPs are provided here, from raw materials to intermediates (if applicable).
Executed Batch Records: Completely filled Batch Manufacturing Records of at least one batch need to be included. Certified translations are required.	Validation Scheme: EU specific validation scheme according to CPMP/QWP/848/96 is presented here.
Comparability Protocols: Evaluation showing the risks and applicable measures of any deviations from the provided information. Beneficial for future changes.	TSE table and certificates: Information on TSE is presented in tabulated format in this section. TSE certificates are an attachment to this table.

Conclusion

Though both regions are members of the ICH and therefore share many scientific and regulatory guidelines, there are significant differences in how these are interpreted and implemented.

The US quality module explicitly contains GMP and batch record documents, while the European authorities explicitly ask to exclude any GMP documents. Therefore information provided in these need to be presented in abstracted narration in the CMC sections. As a benefit in the EU, GMP life-cycle doesn't cause regulatory variations.

A significant part in European CMC writing therefore is the abstracting and minimizing data.

The CMC sections of a US application disclose every possible product flaw by presenting the maximum amount of available data. In contrast the European quality part focusses on identifying the critical characteristics of the product and presenting data in regard to these.

In summary it can be concluded that due to the differences in historical expectations and culture at the relevant health authorities, the same legal format and regulatory guidance (CTD/ICH:M4) result in vastly differing quality dossiers in the United States and Europe.

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