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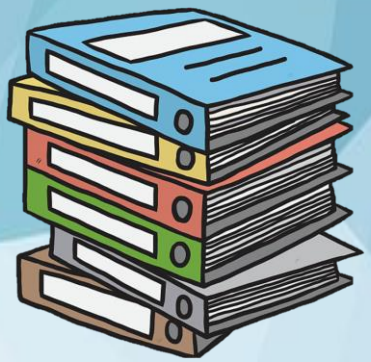
Should CMC be a Challenge for IND Preparation?



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Dedicated for Approval ®

What is CMC?

Chemistry, Manufacturing and Controls (CMC) is a significant and necessary part of a pharmaceutical application. The manufacturing process, facilities and process controls, product characteristics, analytical testing procedures, and stability testing and results for the Drug Substance(s) and Drug Product are included in the CMC section of pharmaceutical dossier. Sufficient CMC information is needed to ensure the drug's safety, identity, strength, quality and purity.

Why CMC is important?

CMC activities pervade the drug development life cycle beginning with drug discovery and will last even after the drug approval. For example, manufacturing processes are designed and performed at an early stage to produce small batches of Drug Substance and Drug Product for early phase clinical study and must be kept updated during the whole process of drug development. Ultimately, the manufacturing process will go through scale up stage and ensure that the larger batches of product are produced at the same level of quality to support commercialization after drug approval. Even after the drug reaches the NDA or BLA approval stage, the manufacturing process will be updated to meet the updated requirements from regulatory authorities as well as to keep up with the evolution in drug production technology. This is why CMC documents are also called "living documents" in pharmaceutical dossiers.

On the other hand, in CMC lies the foundation for drug development. For instance, proper analytical methods are developed and validated to monitor the product during manufacture. In-process controls are set up to control the quality of the Drug Substance and Drug Product which will then be used in non-clinical and clinical studies. The physical and chemical properties of the Drug Substance are characterized, and the impurity profile is determined to support the non-clinical studies, especially the animal toxicology studies. The drug formulation is developed with the goal of delivering a fully potent (stable) test article throughout the clinical studies. This is an example of the importance of CMC in drug development.

What CMC information and where is it needed in the IND application?

Currently, pharmaceutical dossiers for drug applications (IND, NDA, BLA, etc.) are submitted in Common Technical Document format. CMC contents are part of the Module 3 Quality Section. Module 3 is divided into four sections including two main sections which are Drug Substance (3.2.S) and Drug Product (3.2.P), an Appendices section (3.2.A) and the Regional Information Section (3.2.R). The summary contents for the two major sections (3.2.S and 3.2.P) are shown in the table below :

Dossier Section		Contents
3.2.S Drug Substance	3.2.S.1 General Information	This section can be considered as a brief summary section for Drug Substance. Chemical name, chemical structure, physicochemical and other relevant properties particularly those that could affect pharmacological or toxicological safety should be included in this

Dossier Section		Contents
		section. The determination of those properties is usually included in Section 3.2.S.3.
	3.2.S.2 Manufacture	This section contains information related to the Drug Substance manufacturing process. This information can be divided into two parts: 1. How the Drug Substance was manufactured; 2. How the Drug Substance quality is controlled. The flowchart and narrative are usually presented for the manufacturing process. The in-process controls, control for starting materials and critical steps are included to ensure Drug Substance quality. The analytical methods supporting quality control are shown in Section 3.2.S.4 and the impurity information can be found in Section 3.2.S.3.
	3.2.S.3 Characterization	This section is divided into two parts: 1. How the target Drug Substance is characterized (physical properties and chemical identity); 2. What potential impurities are in the Drug Substance. Usually spectral analyses, information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should be included. The impurities section describes all impurities that are observed in the Drug Substance. These include organic impurities, inorganic impurities, and residual solvents, etc.
	3.2.S.4 Control of Drug Substance	This section is divided into three parts: 1. The specification and analytical results for all batches of Drug Substance in IND studies; 2. Methods of Drug Substance analysis; 3. Justification for the analytical method and specifications. The core idea for this section is control of the Drug Substance quality.
	3.2.S.5 Reference Standards or Materials	Information on the reference standards or reference materials used for testing of the Drug Substance is provided in this section.
	3.2.S.6 Container Closure System	This section contains information about the container closure systems for the Drug Substance including the identity of materials of construction of each primary packaging component, and their specifications.
	3.2.S.7 Stability	This section contains stability information for the Drug Substance, including the Stability study protocol, analytical methods (if not the same as presented in Section 3.2.S.4) and results. Ideally stability tests are conducted under various storage conditions including long-term, accelerated and stress test conditions. Stability studies are very important for proper handling and shelf life determination.
3.2.P Drug Product	3.2.P.1 Description and Composition of the Drug Product	A description of the Drug Product and its composition should be provided. The information provided should include: Description of the dosage form, Composition, Description of accompanying reconstitution diluents, Type of container and closure

Dossier Section		Contents
	3.2.P.2 Pharmaceutical Development	This section contains the Drug Product development information. Several aspects are especially important as follows: 1. How the formulation was developed. 2. Are other materials (such as excipients, container, diluents, etc.) compatible with Drug Substance. 3. How the manufacturing process of Drug Product was developed.
	3.2.P.3 Manufacture	This section contains all the necessary information related to the manufacture of Drug Product. This information can be divided into two parts: 1. How the Drug Product was formulated and manufactured; 2. How the Drug Product quality is controlled. The flowchart and narrative are usually presented for the manufacturing process. The in-process controls, control of critical steps and intermediates are included to ensure Drug Product quality. The analytical methods supporting quality control and the information of newly generated impurities in Drug Product due to the manufacturing process can be found in Section 3.2.P.5.
	3.2.P.4 Control of Excipients	Excipients are a very important part of the Drug Product. If the excipients are in the national pharmacopeia, no specific control information is needed. If there are novel excipients, detailed information must be provided. Special attention should also be given to excipients from human or animal origin.
	3.2.P.5 Control of Drug Product	The structure of this section is very similar to Section 3.2.S.4 (Drug Substance)., The control information for the Drug Product is provided in this section. In addition, if any impurities are generated during the manufacture of the Drug Product, information about those impurities is provided in this section.
	3.2.P.6 Reference Standards or Materials	Information on the reference standards or reference materials used for testing of the Drug Product should be provided if not previously provided in 3.2.S.5
	3.2.P.7 Container Closure System	This section contains information about container closure systems for Drug Product. The structure is the same as Section 3.2.S.6. (Drug Substance)
	3.2.P.8 Stability	This section contains the information on stability testing for the Drug Product. The structure is the same as Section 3.2.S.7. (Drug Substance)

What is FDA's requirement for CMC section in the IND application?

Since the CMC section is very essential for the IND application, FDA and ICH have published guidance documents to help sponsors organize their CMC information and issues. ICH quality guidelines Q1 to Q6 are most relevant to the IND application. FDA also provides more specific guidance to certain specific CMC topics, such as new types of drugs (gene therapy, bispecific antibody, etc.), drugs which include nanomaterials, CMC requirements for later phases and so on.

Since the CMC dossier is a living document, maintaining an accurate historical database of CMC information consistent with the current guidances is very important.

Although FDA and ICH have provided detailed guidance for CMC topics, the majority of those guidances are designed for NDA or BLA applications. The information that should be provided at IND stage may be very different. For example, the manufacturing process at IND stage may be very different from the NDA stage. The purification methods that are relatively complex such as chromatography may be replaced with a more suitable method such as recrystallization. The description of IND manufacturing process may be relatively simple compared to NDA stage. The in-process controls will become more stringent during the development of the manufacturing process as experience is gained over time. In this case, FDA's requirement for the IND manufacturing process may be more permissive when compared to the marketing application (NDA, BLA). Regulatory authorities generally expect progression to more extensive and more detailed CMC information and stricter quality control during drug development. At the IND application stage, FDA requirements for CMC will be suitable for small batches for Phase 1 studies, which are carefully monitored for safety in a small number of patient or subjects. The CMC contents such as impurities control that may affect drug safety will be the main reviewing focus of FDA. However, the focus of FDA review of CMC information at the IND stage is dependent on many factors depending on the molecule, the formulation and administration, the indication and the pre-clinical safety profile. That is where Aleon's experience can help you to prepare the CMC section.

How can Aleon help you to solve CMC challenges during IND preparation?

As a leading Regulatory Affairs consulting firm, Aleon staff have successfully prepared numerous IND applications and has extensive experience with NDA/BLA approvals. A strong CMC team with solid chemistry background as well as a rich regulatory experience are available to you at Aleon. In addition, Aleon's vast experience and knowledge not only can support solving your CMC issue but also facilitate your whole IND application process. We have an extensive understanding of FDA review philosophy for CMC and are willing to provide help to clients with their IND applications. One-stop service is another benefit that Aleon can offer to our clients. Our dedicated team will help you starting from project initiation, gap analysis, pre-IND meeting CMC document preparation, IND Module 3 preparation, amendment submission, and all the way to NDA/BLA approval. Since CMC documents are "living" throughout the whole drug development process, Aleon's excellent maintenance and record service will help you keep track of every step towards the drug approval. In addition, a strong team of experienced consultants at Aleon who have more than twenty years' work experience either in big pharma or at FDA will provide you the best regulatory strategy and help to smooth your regulatory pathway. Choose Aleon, we will give you a seamless experience for your drug development process.

Should CMC be a challenge for IND preparation?

We hope that you have found the answer after reading this position paper.

We like to think that answer we have here for our clients is that CMC need not be a concern for our clients. Even though the CMC section contains much complex, technical information and the

regulatory guidances are numerous and detailed, our experienced and dedicated team will help you work through all the difficulties. If you have any questions about CMC, Aleon is always here to help.

Your success is our honor!

Reference:

FDA & ICH guidance:
M4Q: The CTD - Quality
Q1A(R2) Stability Testing of New Drug Substances and Products
Q3A(R) Impurities in New Drug Substances
Q3B(R) Impurities in New Drug Products
Q3C Impurities Residual Solvents
Q11 Development and Manufacture of Drug Substances

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If you want to know more about Aleon, please do not hesitate to give us a call or e-mail.