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Session Report

Roads Leading to Approval: The Right Level of Detail for CMC Submissions

Speakers
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What is the right level of detail for submissions? Too much detail in submissions can make post approval changes a nightmare. Too little detail can lead to refusal of your application. How do you determine the right level for your submission? There are many considerations to be made when completing a new drug application (NDA) or a biologics license application (BLA).

Forwood began by discussing the right level of detail for an NDA. Every submission has a unique level of detail required. The following points are considerations when deciding the appropriate level of detail:

- Items discussed in your presubmission meetings with the US Food and Drug Administration (FDA). Make sure your submission covers any points discussed by your FDA manager in meetings for the investigational new drug application (IND), NDA, or BLA.
- Understand which modules are regulatorily binding. These are modules that will require a post approval submission if changes are made to them. Having too much detail in these modules can adversely impact your ability to make post approval changes to your product.
- Develop a relationship with the FDA manager for your project. This relationship can help with making submissions geared toward the FDA reviewer.
- Comparability protocols (to be discussed later).

The right level of detail is dependent upon the complexity of the product. The higher the complexity, the more detail is needed to demonstrate the details of the product. Small molecule drug products are more well-known and usually require less detail than large molecule products (eg, vaccines, biologics, and gene and cell therapy products).

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q12, Jan 2020, Appendix 1[1] (ICH Q12) is the guidance used to give examples of typical regulatorily binding modules. Forwood reviewed several examples the electronic Common Technical Document (eCTD) Module 3, which details typical regulatorily binding modules (established conditions) from the ICH Q12. Forwood also discussed post approval changes in manufacturing, all of which must be reviewed by someone in Chemistry, Manufacturing, and Controls (CMC) Regulatory Affairs to determine if there is a change in the established conditions in the existing application(s). She discussed the different pharmacopeia (ie, the books describing drugs, chemicals, and medicinal preparations as the standard in each region): the United States Pharmacopeia (USP), European Pharmacopeia (Ph. Eur.), British Pharmacopeia (BP), and Japanese Pharmacopeia (JP). There are differences between the USP, Ph. Eur., BP, and JP; however, ICH is working on reducing these differences.

Rousselin spoke on submissions of large molecules (biologics) and vaccines. Biologics are grown and harvested rather than synthesized, which poses issues. Biologics are exponentially larger than small molecules, which makes them harder to identify, characterize, and isolate. They are also susceptible to contamination, which presents regulatory challenges. There is increased detail necessary for large molecule applications, and these applications can be as much as twice as long as those of small molecule applications. Rousselin discussed the increases required in regulatory detail for biologic applications. He specifically spoke of ICH Q12 module 2.3, which is quality overall summary. He also discussed some parts of module 3 that could have increased regulatory detail for a biologic application. Contamination and stability are very important to consider, and process validation is a requirement for a BLA. There is a level of redundancy between modules 2 and 3 that can be required for large molecules. Finally, the ICH Q12 module 3.2.A, appendices are to show how effective your aseptic quality controls are.

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Rousselin then detailed the regulation of vaccines, which has similar content requirements to that of a BLA. Most vaccines have long development times that increased from the 1990s to the 2000s[3]. Barriers to vaccine development and approval include limited return on investment in both industry and academia, and limits of healthy individuals to take the vaccines. There have been less than 25 vaccines licensed by the FDA over the last 10 years. However, the FDA has instituted regulations to accelerate approvals for serious conditions. These lead to accelerated approvals, fast track evaluations, and breakthrough therapy designations. Two FDA regulatory programs authorize access pre-FDA approval: Expanded Access (Compassionate Use)[4] and Emergency Use Authorization[5]. This has accelerated approvals to approximately 1 per year in recent years.

Vaccines have 3 classes: viral vector, mRNA, and DNA. mRNA vaccines could be the dawn of a new age because they have certain advantages: they are easier to manufacture, are noninfectious, and they have versatility across many therapeutic areas, including cancer and gene therapy. These new therapeutics will require new approval protocols.

Forwood then spoke on comparability protocols (CPs), a comprehensive written plan to assess the effect of potential or known changes to be made post approval. CPs may be submitted as part of the original application or as a post approval change. CPs assist the applicant with knowing what studies and tests are needed when post changes are to be made. CPs can help with these post approval submissions by having an agreed-upon list of what will be needed, what will need to be contained in the submission, and they may even reduce the regulatory burden for post approval submissions.

Forwood spoke lastly on drug master files (DMF(s)). When there are 2 or more manufacturing partners; a DMF allows each party to protect their intellectual property. The DMF holder files the DMF with the FDA and includes a letter of authorization (LOA) in their DMF (or may amend an existing DMF with an LOA), allowing the partner submitting the NDA (or supplemental NDA) to reference the information within the DMF. There are currently 4 different types of DMFs:

1. Type 2 Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation; or Drug Product;
2. Type 3 Packaging Material;
3. Type 4 Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation, and;
4. Type 5 FDA-Accepted Reference Information.[2]

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