

Effective ICH Q8 Pharmaceutical Development Reports

INTRODUCTION

The International Conference on Harmonization (ICH) Common Technical Document (CTD) format is the submission standard for new and abbreviated drug product applications in the United States, the European Union and Japan. One of the significant sections of the CTD is the Pharmaceutical Development Report (PDR). A complete PDR is essential to provide a comprehensive understanding of the product and process for the FDA application reviewers and inspectors. The information in the PDR is based upon the documentation generated during the formulation and process development phase of drug development.

The ICH Q8 and Q8(R1) Pharmaceutical Development Report guidance documents provide the guidelines for the PDR.^{1,2} As stated in the Q8 guidance, “The Pharmaceutical Development section provides an opportunity to present the knowledge gained through the application of scientific approaches and quality risk management to the development of a product and its manufacturing process.” The PDR can, and should, be updated over the lifecycle of the product as new knowledge of the product is obtained.

There are six critical sections to PDR development listed in the Q8 guidance document. Each section addresses a specific component or process in the development process, including:

1. Components of the drug product
2. Information about the drug product formulation development, overages, and physiochemical and biological properties
3. Describes the manufacturing process development
4. Rationale for the choice of the drug product container closure
5. Rationale for selecting the preservative systems and performing, or not performing, the compendial microbial limits and antimicrobial effectiveness tests
6. Compatibility of the drug product with reconstitution diluents or dilution prior to administration for labelling information

Obviously, the primary goal of the marketer and manufacturer of the drug product is to design and produce a product to meet the intended performance. Thus, the PDR should provide sufficient information to describe the formulation and process development and to substantiate that the product is safe and suitable for the intended use.

The Contract Development and Manufacturing Organization (CDMO) is critical to the timely development of the PDR documentation. Furthermore, working with a contract development partner requires close communication and an early understanding of the PDR process by all entities to ensure clear and consistent documentation.

RATIONALE

To provide the necessary data and rationale for the PDR, the development process should determine how variation of the parameters and attributes can affect the drug product and provide enhanced knowledge of the effects over the variation range of the parameters. Essential to this analysis is the identification of the critical product quality attributes and the critical process parameters. This includes defining the target product profile, the critical quality attributes and the appropriate manufacturing process. The controls that are required for the drug substance, excipients, container closure, and/or the manufacturing process to achieve and maintain the critical attributes are provided. These can be determined by prior knowledge, employing design of experiments methodologies, and/or understanding the functional relationships linking the material attributes to the process parameters. This results in defining of a design space for the drug product, within which the product will meet the quality attributes. This scientific-based, systematic approach to development is referred in the Q8R1 as “Quality by Design” (QbD).

SOLUTION

Section 1

The first section presents the components of the drug product, i.e., the drug substance and the excipients. The physiochemical and biological properties that can influence the performance of the drug product and its manufacturing process are discussed for the drug substance and the excipients. An example of these properties for semisolid products is particle size. In addition, data supporting the compatibility of the drug substance and excipients, as well as the excipients with each other are provided. For the excipients, the data should demonstrate their ability to meet their functional requirements in the drug product for the shelf life of the product. Often this analysis is derived from the product stability data.

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Section 2

The second section presents the information about the drug product formulation development, overages, and physiochemical and biological properties. This includes a summary of the development of the formulation from the initial concept to the final formulation and provides the justification for the choice of the drug substance, excipients, container closure system, and overages, as well as the critical quality drug product attributes. Comparison of the formulations used in the pivotal clinical batches, primary stability batches, and the commercial formulation are also described. The physiochemical and biological properties important for the safety, efficacy or manufacturing of the drug product are presented. Examples of these properties for semisolids and solutions are pH and viscosity.

Appropriate experiments should be performed in the development stage to provide the rationale for the qualitative and quantitative formulation. The development of the analytical methods, which usually is performed in parallel with the formulation development, should be described as it relates to the assessment of the identity, strength, quality, purity, and potency of the drug substance and drug product during the development process.

Section 3

The third section describes the manufacturing process development. The rationale for the selection, controls, appropriateness of components and equipment, and process design is discussed. The critical process parameters, their monitoring and control, are presented in this section as well as the justification for the drug product specifications. As with the formulation, the differences between the manufacturing processes used for the pivotal clinical trial batches, the primary stability batches and the commercial process are discussed. Data should be provided to show the robustness of the process to reliably produce the quality product. The process development activities should include experiments to provide the rationale for the manufacturing process controls and parameters that provide the basis for the critical process parameters in the process validation protocol.

Section 4

The next section provides the rationale for the choice of the drug product container closure. The materials and design of the container closure and the compatibility of those materials with the drug product are provided. This includes a discussion of requirements such as protection from moisture and light. Appropriate testing described in compendia and regulations must be performed to provide the rationale for the use of the specific container closure. This may include extractables/leachables chemical testing as well as “form, fit, function” testing.

Section 5

The fifth section provides the rationale for selecting the preservative systems and performing, or not performing, the compendial microbial limits and antimicrobial effectiveness tests. This may include testing at the lowest specification for the preservative(s) and testing simulating patient use to justify the efficacy and safety such that the minimum concentration of preservatives is used. The results of the microbial testing substantiate the qualitative and quantitative preservative requirements.

Section 6

The final section discusses the compatibility of the drug product with reconstitution diluents or dilution prior to administration for the labeling information. This includes in-use shelf life at the extremes of the concentration.

CONCLUSION

Meeting the requirements of the Q8 and Q8R1 PDR requires close communication between the CTD applicant and its contracted development partners to ensure that the appropriate data and information is obtained during both the formulation and development processes. The Contract Development and Manufacturing Organization (CDMO) will play an important role in the timely preparation of the PDR documentation. In addition, if more than one entity is involved in the development process, an understanding of the data and documentation that each entity must provide is essential to the preparation of the PDR to provide a cohesive and well written document for the submission. The applicant should ensure that all of the contract entities have an excellent understanding of PDR requirements and the capability to prepare the PDR in the format and content appropriate for the application based upon the guidance documents. This will enhance the success of a favorable review by the regulatory agency.

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FOOTNOTES

1. Guidance for Industry, Q8 Pharmaceutical Development, May 2006,
<http://www.fda.gov/cder/guidance/6746fnl.htm>
2. Q8(R1) Pharmaceutical Development Revision 1, November 2007
<http://www.fda.gov/cder/guidance/8084dft.htm>

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