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INFLUENCE OF (QbR) QUESTION BASED REVIEW TO REVAMP CMC SUBMISSION REVIEW

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ABSTRACT

QbR for CMC evaluation of an ANDA is focused on critical pharmaceutical attributes. When an applicant submits a QOS of CMC that fully addresses the QbR, this helps to assure product quality and may reduce the number of CMC review cycles by enhancing the quality of submissions and reviews through the use of a standardized set of critical questions. Question-based review (QbR) is a science and risk-based approach to the Chemistry, Manufacturing, and Controls (CMC) evaluation of an Abbreviated New Drug Application (ANDA) to ensure pro duct quality. The QbR questions and this guidance document, in order to adequately assess the safety, effectiveness, and quality of the product. This new QbR system incorporates quality by design and implements risk-based assessment. It recommends that ANDAs be submitted using the Common Technical Document and include the Quality Overall Summary (QOS) that addresses all the QbR questions. This retrospective study explains about the CMC and its challenges and importance of QbR and how QbR will transform the CMC review.

KEYWORDS: QbR – Question based Review, CMC – Chemistry manufacturing Control, QoS – Quality over all summary, ANDA- Abbreviated new drug.

1. INTRODUCTION

Pharma R&D investment has increased 62 percent in the last decade, but the number of new drugs approved is 22 percent lower than the previous decade. The failure rate in phase III, the most expensive part of pharma R&D, is 40 percent. A Data monitor study of 346 NDAs found that 42 percent of submissions received a complete response letter, resulting in a median delay in approval of 13 months. Cost cutting and the retirement of baby boomers with deep expertise have resulted in a shortage of in-house experts with the savvy to drive innovation and gain regulatory approvals.[1]

The registration dossier for medicines is an important document which is submitted for review to regulatory agencies by pharma companies for approval to market their medicines. Utmost care should be taken during its compilation and filing as it plays a direct role in earliest possible availability of medicines in the market which in turn translates into business for the company.[2]

Global chemistry, manufacturing, and control (CMC) dossiers are critical to a successful regulatory submission. The creation and subsequent assembly of the CMC dossier requires an orchestrated cooperation between R&D, clinical, regulatory, sales/marketing, and other groups who will have an input into this important document. Managing the construction of a clear, concise dossier can be a daunting task, but it doesn't have to be. A simple understanding of best practices surrounding the creation and presentation of the CMC section will make for a successful submission.[3]

QbR is an enhanced pharmaceutical Quality assessment system. It is a general framework for CMC assessment of the ANDA. A successful dossier submission can prevent the delay in product registration. An effective documentation and CMC submission prevent the non-compliance, more than 50% of the dossier comprising of CMC documentation of substance (API) and product part (FPP). CMC regulatory compliance is seen as a process of governance which ensures CMC practices are carried out in agreement with regulatory agencies requirements and expectations. Since such requirements and expectations change with time, a function of CMC regulatory compliance is to ensure that all CMC practices are updated accordingly.

Furthermore, CMC Regulatory compliance is to ensure that if the pharmaceutical organisation has made any CMC specific commitment to the regulatory agencies, either verbally or in writing, that such CMC practices are carried out.

A series of questions that focus on the critical information needed to evaluate the product quality. Acceptable responses to the questions will satisfy the CMC filing CFR - FDA.

QbR contains the important scientific and regulatory review questions that capture key aspects of *f* Drug substance, excipients, formulation, process design, manufacture, control, container closure system, reference materials, and stability.

2. Challenges in CMC

Preparing a chemistry, manufacturing, and control (CMC) dossier can be a daunting task. It is a detail-oriented undertaking, and as the saying goes, the devil is in the details. Whether you are assembling the CMC dossier for an Investigational New Drug (IND) application, New Drug Application (NDA), Drug Master File (DMF), Biologics License Application (BLA), or Abbreviated New Drug Application (ANDA), organization of your information and data is paramount. Assembling a CMC dossier is information and document-based.[4]

Chemistry, Manufacturing and Control (CMC) compliance initiatives in the life sciences industry involves comparing registered information with manufacturing details. It aims to resolve any gaps in data and reduce the risk of product recall or other penalties. To increase the success and value of this resource-intensive activity, existing CMC compliance initiatives need to be supplemented by best practices and enabling technology.[5]

Chemistry, Manufacturing, and Controls (CMC) Regulatory Affairs (RA) plays a pivotal role in the development, licensure, manufacturing, and on-going marketing of pharmaceutical products. In this role, CMC RA professionals help ensure that pharmaceutical products are consistently effective, safe and high quality for consumers. During an interview with Ashton Tweed, CMC RA career veteran Frederick A. "Simon" Golec, Jr., PhD, shares his insight on the most important CMC issues companies face today. He also offers some great advice for those considering a career in this area.[6]

CMC regulatory affairs operations struggle with complex and rapidly growing responsibilities. Chemistry, manufacturing, and controls (CMC) regulatory affairs assume a significant share of these complex functions within pharmaceutical regulatory affairs. CMC regulatory professionals are responsible not only for CMC-related documentation for review by health authorities around the world but also documentation that addresses the frequent changes in drug substance and drug product manufacturing sites. CMC regulatory professionals also provide annual reports and renewals to ensure continued market access for a pharma company's product portfolio. These professionals also help the manufacturing sites remain "in compliance." In addition, the increasing requirements of health authorities around the world for greater detail on the CMC section of pharmaceutical marketing applications is putting more demands on industry and CMC regulatory professionals.

Chemistry, Manufacturing and the Controls (CMC) of a medicinal product is the body of information that defines not only the manufacturing process itself but also the quality control release testing, specifications and stability of the product together with the manufacturing facility and all of its support utilities, including their design, qualification, operation and maintenance.

Within the EU, the marketing authorisation holder and Qualified Person will be held responsible if the manufacture of a medicinal product is not undertaken according to the details supplied in the CMC section (CTD, Module 3 or equivalent) of the approved dossier. The legal framework in the EU is defined in Directive 2001/83/EC, as amended, with key statements found within Articles 20, 23 and 51. Similar principles apply to the US and other international markets.[7]

2.1 Contents of CMC

Chemistry, Manufacturing and Controls (CMC) is the body of information that defines:

- The manufacturing facility and all of its support utilities (their design, qualification, operation, maintenance).
- The process equipment materials used in manufacturing (design, qualification, validation, operation, maintenance).
- The manufacturing process itself (definition, validation, consistency).
- The personnel involved in manufacturing and quality (adequate numbers and competency).
- The chemistry of product (characterization and proof of structure).
- Quality control release testing, specifications and stability of the product.
- Quality Assurance release and rejection of materials and product.
- All of the controls, documentation, and training necessary to ensure that all of the above is properly and effectively carried out.

2.2 Importance of CMC

- To assure that the drug sold to the public will have quality attributes similar to those of the drug demonstrated to be safe and effective.
- To assure that the quality of the drug meets appropriate standards and is consistent.
- To assure that the drug you are using is the drug on the label.

2.3 CMC Critical elements

How and where is the drug made?
How are raw materials tested and monitored?
What control procedures are in place to assure product consistency and quality?
Are quality attributes adequately identified and characterized for the product?
Are the test methods used to monitor product quality appropriate?
How long does the product maintain its quality after it is made (shelf life/expiry)?[8]

2.4 Management of Worldwide Regional Regulatory CMC Requirements - An Approach by Creation of a CMC Database

The pharmaceutical market covers more than 100 countries. The market can be divided, based on its regulatory diversity into the regulated and the emerging markets, the latter covers regional worldwide countries.

Regulatory diversity is tremendous when comparing individual country requirements and it has become extremely complex to fulfil each country's specific requirements. Having knowledge of the guidelines is a pre-requisite and basic tool for successful submissions.

Most international companies analyse the differences and similarities between the regulatory requirements and pharmaceutical legislations of regional countries to develop regulatory strategies in order to avoid submission surprises. However, in many international companies there is no robust process in place and heterogeneous approaches for regional submissions exist, e. g. what to be provided with the initial submission package.

One of the major problems here is the management of the information overload and the establishment of a system from which the collected regulatory requirement information can be directly applied for successful submissions. Thereby, resulting in a scenario that proactive regional country specifics are assured.[9]

2.5 Solution

- **CMC strategy:** strategy and planning from product development to new product filings, relevant health authority meeting support and interaction, due diligence, site rationalization, and submission coordination
- **CMC authoring:** Modules 2 and 3, NDA/MAA and IND/CTA, line extensions, dossier formulation/translation, and much more
- **Lifecycle submissions:** License renewals, annual reports, support of government and hospital tenders, CPPs, legal entity changes, and ancillary document collection/compilation
- **Dossier review and compliance:** Data review, dossier consistency, compliance audit, gap analysis and remediation, pre-approval preparation and pre-audit, due diligence assessment, and GMP inspection.[10]

2.6 CMC Development Strategies for Small Pharma

For small molecule new chemical entities (NCEs) in development, the value drivers are typically intellectual property, safety and efficacy. The CMC profile is often less important unless there is a major weakness in the molecule's properties, e.g., very low solubility, poor stability, or inappropriate pharmacokinetic (PK) profile. In contrast, for an active substance that is a large biomolecule (multiple molecular structures, high molecular weight, and produced by biological processes) the means of administration into human and animal physiological systems may be a valuable part of the asset. Additionally, there are many routes of administration for small molecule NCEs where the delivery technology comprises a key part of the value, inhaled drugs being an obvious example. However, for many small molecules, CMC development principally enables non-clinical and clinical development, and does not drive asset value.[11]

3. Importance of QbR

The ever increasing workload at the Office of Generic Drugs (OGD) within the US Food and Drug Administration's Centre for Drug Evaluation and Research (CDER) has led the office to develop a number of strategies to streamline the review process. One such strategy was the introduction of Question-Based Review–Quality Overall Summary (QbR–QOS).

3.1 QbR transform the CMC Review

The Office of Generic Drugs' (OGD) is developing a question-based review (QbR) for the Chemistry, Manufacturing, and Controls (CMC) evaluation of an Abbreviated New Drug Application (ANDA) that is focused on critical pharmaceutical quality attributes. The QbR initiative began in early 2005 with the development of a revised review template and is approaching the early implementation phase as we gain feedback through wide internal and external discussions.

The QbR will transform the CMC review into a modern, science and risk-based pharmaceutical quality assessment that incorporates and implements the concepts and principles of the FDA's Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach and Process Analytical Technology initiatives. The main objectives of this enhanced review system are to:

- Assure product quality through design and performance-based specifications,
- Facilitate continuous improvement and reduce CMC supplements through risk assessment,
- Enhance the quality of reviews through standardized review questions,
- Reduce CMC review time when sponsors submit a quality overall summary that addresses the QbR.

OGD's QbR was designed with the expectation that ANDA applications would be organized according to the Common Technical Document (CTD), a submission format adopted by multiple regulatory bodies including the FDA. Generic firms are strongly recommended to submit their ANDAs in the electronic CTD format to facilitate the implementation of the QbR and to avoid undue delays in the approval of their applications. OGD will keep all stakeholders informed of the changes through this office website and our continued dialogue with the Generic Pharmaceutical Association, and other stakeholders.

3.2 Q b R based review for CMC Submission

2.3.S DRUG SUBSTANCE

2.3.S.1 Description and Composition

1. What are the nomenclature, molecular structure, molecular formula, CAS number, molecular weight, and pharmacological class of the drug?
2. What are the physical, chemical, biological and, if applicable, mechanical properties including physical description, pKa, chirality, polymorphism, aqueous solubility as a function of pH, hygroscopcity, melting point(s), and partition coefficient?

2.3.S.2 Manufacture

2.3.S.2.1 Manufacturer

3. Who manufactures the drug substance? List each participant and facility involved in drug substance manufacturing/testing activities and clearly state their function. List the date of the last FDA inspection of each facility involved and the result of the inspection. Has the manufacturer addressed all concerns raised at the FDA inspection?

2.3.S.2.2 Description of the Manufacturing Process and Controls

4. What is the flow diagram of the manufacturing process that shows all incoming materials, reagents, reaction conditions, in-process controls and, if appropriate, any reprocessing/reworking/alternative processes?
5. If applicable, what online/at line/in line monitoring technologies are proposed for routine commercial production that allows for real-time process monitoring and control? Provide a summary of how each technology was developed.

2.3.S DRUG SUBSTANCE

2.3.S.2.3 Control of Materials

6. What is (are) the starting material(s) for the manufacturing process and how would changes in starting material quality and/or synthesis/source be controlled to minimize adverse effects on the drug substance quality?
7. What are the starting material specifications and how are they justified?
8. What are the specifications for reagents, solvents, catalysts, etc.? What are the critical attributes for these materials that impact the quality of the final drug substance? 2.3.S.2.4 Control of Critical Steps and Intermediates
9. What are the critical process parameters (CPPs) and how are they linked to drug substance quality?
10. What are the in-process controls (IPCs) or tests, associated analytical procedures, and acceptance criteria for each control?
11. What are the specifications for the intermediate(s)? 2.3.S.2.5 Process Validation and/or Evaluation
12. What process validation and/or evaluation information is provided, if any?

2.3.S.2.6 Process Development

13. What development and scale-up information supports the commercial process and control strategy?
14. How is the drug substance structure characterized?
15. What are the potential impurities (e.g. related substances, degradants, inorganic impurities, residual solvents) in the drug substance? Which of these impurities are potentially genotoxic?

2.3.S.4 Control of Drug Substance

16. What is the drug substance specification and what is the justification? Does the specification include all of the critical drug substance quality attributes?
17. For each test in the specification, provide a summary of the analytical procedure(s) and, if applicable, a summary of the validation or verification report(s).
18. How do the batch analysis results compare to your proposed specification? Provide a summary of the batch analysis results.
19. What is the proposed control strategy for the drug substance manufactured at commercial scale? What are the residual risks upon implementation of the control strategy at commercial scale?
20. How are the drug substance reference standards obtained, certified and/or qualified?

2.3.S.6 Container Closure

21. What container closure system(s) is proposed for commercial packaging of the drug substance and how is it suitable to ensure the quality of the drug substance during shipping and storage?
22. What are the stability acceptance criteria? If applicable, what is the justification for acceptance criteria that differ from the drug substance release specification?
23. What is the proposed retest period for the drug substance? What drug substance stability data support the proposed retest period and storage conditions in the commercial container closure system? How does statistical evaluation of the stability data and any observed trends support your proposed retest period?
24. What are the post-approval stability protocols and other stability commitments for the drug substance?

2.3.P DRUG PRODUCT (QOS – CTD format)

2.3.P.1 Description and Composition

1. What is the description of the proposed commercial drug product? What are the components and composition of the final drug product as packaged and administered on both a per unit dose and %w/w basis? What is the function(s) of each excipient?
2. Does any excipient exceed the FDA inactive ingredient database limit for this route of administration calculated based on maximum daily dose? If so, please justify.
3. If applicable, what are the differences between this formulation and the Reference Listed Drug (RLD) formulation?

2.3.P.2 Pharmaceutical Development

4. For 505b(1) applications, what is the rationale for selecting the proposed dosage form for the drug product? For 505b(2) and 505(j) applications, what are the characteristics of the listed/reference listed drug product? What is the Quality Target Product Profile (QTPP) of the finished product based on the proposed indication and patient population? How is the QTPP justified?
5. What are the quality attributes of the finished product? Which quality attributes are considered critical quality attributes (CQAs)? For each CQA, what is the target and how is it justified?
6. What is the approach for meeting the CQAs related to clinical performance? If applicable, what in vitro bioperformance evaluations (i.e. disintegration, dissolution, diffusion, flux assay, etc.) were used during pharmaceutical development to ensure clinical performance?

2.3.P.2.1 Components of the Drug Product

2.3.P.2.1.1 Drug Substance

7. What are the physical, chemical, biological and, if applicable, mechanical properties of the drug substance including physical description, pKa, chirality, polymorphism, aqueous solubility as a function of pH, hygroscopicity, melting point(s), partition coefficient and, when available, BCS classification?
8. What is the drug substance specification used to accept the incoming drug substance batches and how is it justified? For each test in the specification, provide a summary of the analytical procedure(s) and, if applicable, a summary of the validation or verification report(s). 2.3.P.2.1.2 Excipients
9. What evidence supports excipient-drug substance compatibility and, if applicable, excipient-excipient compatibility?
10. What is the rationale for the excipient selections? 2.3.P.2.2 Drug Product
11. What aspects of the formulation were identified as potentially high risk to the drug product performance?
12. What formulation development studies were conducted? What attributes of the drug substance, excipients, and in-process materials were identified as critical and how do they impact the drug product CQAs?
13. How does the proposed commercial formulation differ from the formulations used during bioequivalence and/or clinical studies? What is the rationale for the formulation change? What biopharmaceutics evaluations (comparative dissolution, bioequivalence studies, biowaivers, etc.) support the formulation changes and link the development formulations to the proposed commercial formulation?

2.3.P.2.3 Manufacturing Process Development

14. What is the rationale for selecting this manufacturing process for the drug product?
15. What is the potential risk of each process step to impact the drug product CQAs and how is the risk level justified?
16. For each potentially high risk manufacturing unit operation:

a) What input material attributes and process parameters were selected for study and what are the justifications for the selection?
b) What process development studies were conducted? Provide a summary table listing batch size, process parameter ranges, equipment type and estimated use of capacity.
c) What process parameters and material attributes were identified as critical and how do they impact the drug product CQAs?
d) How were the process parameters adjusted across lab, pilot/registration, and commercial scale? What are the justifications for any changes?

17. If applicable, what online/at line/in line monitoring technologies are proposed for routine commercial production that allows for real-time process monitoring and control? Provide a summary of how each technology was developed.

2.3.P DRUG PRODUCT

2.3.P.2.4 Container Closure System

18. What specific container closure system attributes are necessary to ensure drug product integrity and performance through the intended shelf life? If applicable, what are the differences in the container closure system(s) between this product and the RLD?
19. How was the container closure system(s), including bulk containers, qualified for suitability (protection, compatibility, safety, and performance)?

2.3.P.2.5 Microbiological Attributes

20. When applicable, what microbiological attributes were evaluated on the finished product?

2.3.P.2.6 Compatibility

21. If applicable, what supportive data demonstrates the compatibility of the drug product with the means of administration (e.g. additives and/or diluents, other co-administered drugs, dosing device)?

2.3.P.3 Manufacture

22. Who manufactures the drug product? List each participant and facility involved in drug product manufacturing/testing activities and clearly state their function. List the date of last FDA inspection of each facility involved and the result of the FDA inspection. Has the manufacturer addressed all the concerns raised at the FDA inspection?
23. What is the commercial batch formula and how does it differ from the registration batch formula? Please provide justifications for any differences.
24. What is the flow diagram of the manufacturing process that shows all incoming materials, processing steps/unit operations, and in-process controls?
25. What is the detailed process description including process parameters, material attributes of raw materials and intermediates, equipment type, batch size, in-process controls including acceptance criteria and any proposed reprocessing?
26. What in-process sampling strategies and methods are used to monitor in-process material attributes that have a potential to affect the drug product quality?
27. What are the in-process test results for each process step of the registration batches? What are the differences, if any, in the in-process controls for the registration batches and the intended commercial batches? What are the justifications for these differences?

2.3.P.4 Control of Excipients

28. What are the excipient specifications and how are they justified? How do the proposed acceptance criteria for the material attributes of the excipients ensure the consistency of the process and quality of the final drug product?

2.3.P.5 Control of Drug Product

29. What is the drug product specification, what is the justification, and how is it linked to the product performance and patient safety? Does the specification include all of the critical drug product quality attributes?
30. For each test in the specification, provide a summary of the analytical procedure(s) and, if applicable, a summary of the validation or verification report(s).
31. How do the batch analysis results compare to your proposed specification? Provide a summary of the batch analysis results.
32. What are the drug product degradants? For each degradant, what is the structure, chemical name, origin, and mechanism of formation? How are the proposed limits justified and/or qualified for safety based on nonclinical studies? What is the control strategy for the potential drug product degradants?
33. What is the proposed control strategy for the drug product manufactured at commercial scale? What are the residual risks upon implementation of the control strategy at commercial scale?

2.3.P.6 Reference Standards or Materials

34. How are the drug product references standards obtained, certified, and/or qualified?

2.3.P.7 Container Closure System

35. What container closure system(s) is proposed for commercial packaging of the drug product? What is the specification?

2.3.P.8 Stability

36. What is the stability specification? If applicable, what is the justification for acceptance criteria that differ from the drug product release specification?
37. What is the proposed shelf-life for the drug product? What drug product stability studies and data support the proposed shelf-life and storage conditions in the commercial container closure system? How does statistical evaluation of the stability data and any observed trends support your proposed shelf-life?
38. What is the post-approval stability protocol and other stability commitments for the drug product?[12]

Benefits

(1) Assure product quality through design and performance-based specifications
(2) Facilitate continuous improvement and reduce CMC supplements through risk assessment
(3) Enhance the quality of reviews through standardised review questions
(4) Reduce CMC review time when applicants submit a QOS that addresses the QbR questions. The QbR was partially implemented in 2006 and is being fully implemented in 2007.

Question-based Review and the Future of Regulatory Submissions

The Question-based Review (QbR) framework, utilized in CDER and CVM integrates important scientific and regulatory review questions into regulatory submissions. The QbR framework facilitates the communication of risk assessment activities, engenders a comprehensive description of product and process development, and envisages an overall control strategy for drug products assessed by the FDA. Industry professionals and regulators benefit reciprocally from the risk-based evaluation of applications and the integration of risk management into development, communication, and management plans.

QbR questions, which can be integrated into the Quality Overall Summary (QOS), should be asked and addressed internally, in real time, during pharmaceutical development activities, rather than writing answers after the fact for the purposes of submission. QbR creates a framework for the applicant to provide a concise knowledge base for review and lifecycle activities, as opposed to the detail-rich Module 3 of the Common Technical Document (CTD). The QbR framework, moreover, incorporates QbD principles.

QbR questions are meant to be flexible; irrelevant questions may be omitted and related questions may be grouped together to provide a concise overview. The FDA has taken efforts to ensure that quality assessments using QbR should not exclude critical information of the submission. A CDER MaPP on QbR has been issued (21). 21. FDA Center for Drug Evaluation and Research (CDER) issued a QbR MAPP for chemistry review.[13]

CONCLUSION

QbR is the basis of the 'e' Submitter template for the CMC Technical Section. It is based on the Common Technical Document - Quality (CTD -Q) format. The Question based Review format includes high level questions and detail questions under each CTD -Q heading. It is a Flexible process that provides the opportunity for "focused" guidance to address common guidance deficiencies or evolving regulatory CMC submission in regulatory affairs.

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