CMC Submission-ANDA and Content of CMC Section

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OFFICE OF PHARMACEUTICAL QUALITY

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Outline

- **INTRODUCTION**
- **Submission Quality**
- **Module 1 – Regional**
- **Module 2 – CTD Summaries**
- **Module 3 – Quality**
  - Module 4, Nonclinical Study Reports
  - Module 5, Clinical Study Reports

} Not a subject of this presentation

Introduction

The presentation will provide information in sections of the Common Technical Document (CTD) format for ANDA applications to assist in preparing a **good**, **complete, high-quality application** to submit to the FDA.

SUBMISSION QUALITY

1. Sufficiently Complete

Acceptable for FILING

2. Application Content

Allows for Complete Technical Review

The Application Should Demonstrate

1. The firm fully understands the product and process.
2. The firm has a robust and consistent manufacturing process.
3. The firm has adequate controls in place from excipients, in-process through stability.

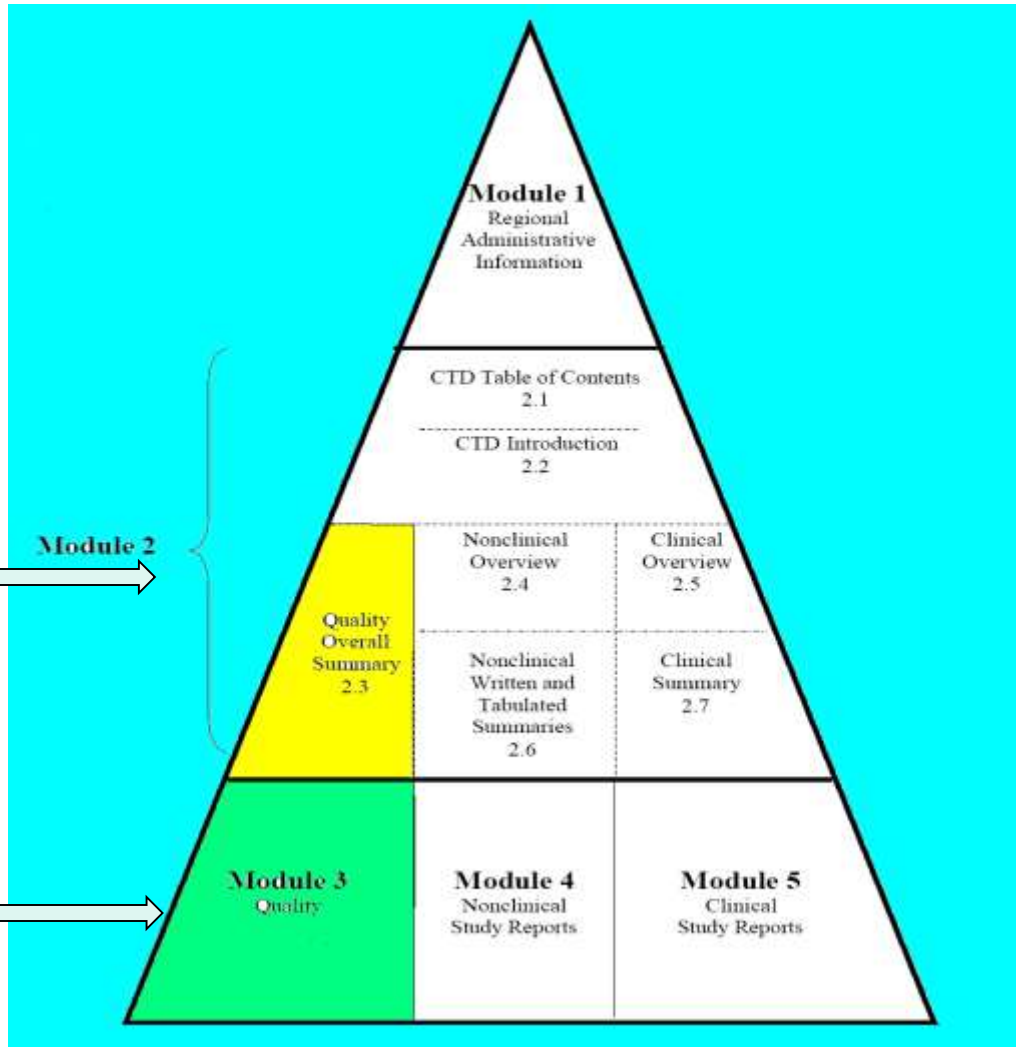
How?

1. Well Organized and logical flow of information.
2. Use Module 2 to tell your product story
3. Provide enough data to support conclusion and decision.

ICH Common Technical Document

QOS
Summary of Critical CMC Elements

Body of Data
Detailed CMC Submission Package



The Integrated Quality Assessment

Under the Office of Pharmaceutical Quality (OPQ), a team-based approach is used to perform the quality assessment of an application. The team consists of:

- Drug substance reviewer(s)
- **Drug product reviewer(s)**
- Process reviewer(s)
- Facility reviewer(s)
- Other technical advisors as needed (Micro)

Application Technical Lead (ATL)

- Oversees the technical content

Regulatory Business Process Manager (RBPM)

- Manages the process

- **Module 1 – Regional**
- **Module 2 – CTD Summaries**
- **Module 3 – Quality**

Module 1 – Regional

- 1.1. Forms
- 1.2. Cover Letter
- 1.3. Administrative Information (contact)
- 1.4. References
- 1.12 Other Correspondence
- 1.14. Labeling
- 1.16 Risk Management Plan (REMS)

Module 2-CTD Summaries

- 2.2. Introduction
- 2.3. Quality Overall Summary(QOS)
- 2.7. Clinical Summary

Module 2

Quality Overall Summary (QOS)

1. **The QOS summarizes what is known about the drug substance(API) in section 2.3.S and the drug product in section 2.3.P.**

2. **It is designed based on QbR (Question based review)**

3. **Use it to tell your product Story and Provides a summary of the chemistry, manufacturing and controls section of the application.**

4. **All information provided in the summary needs to be accurate and supported by information, data, or justification included in Module 3 or other parts of the application.**

Recommendation for Model 2

How were potential impurities identified and characterized?

Imp ID	Compendial Name/IUPAC Name	Structure	Type/ Origin	Proposed limit and where monitored or controlled	Result or Range	Analytical Method (LOD/LOQ)

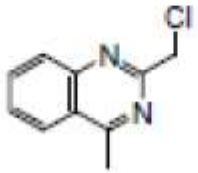
Make sure that the proposed limit is in compliance with ICH Qualification/Identification Threshold and MDD (Maximum Daily Dose) and TDI (Total Daily Intake) to avoid the need for a toxicology consult.

Residual Solvents

Name	Origin	USP<467> Class/Limit	Acceptance Criteria	Result or Range	Analytical Method (LOD/LOQ)
Methanol	Solvents	Class II NMT 3000ppm	NMT 3000ppm/ release testing	646400114: LT 50ppm 646400214: LT 50ppm 646400314: LT 50ppm	GC LOQ 31ppm
Toluene	Solvents	Class II NMT 890ppm	NMT 890ppm/ release testing	646400114: LT 50ppm 646400214: LT 50ppm 646400314: LT 50ppm	GC LOQ 17ppm

Recommendation for Model 2

Potential Genotoxic Impurities (Ref. to ICH M7)

Imp ID	IUPAC name	Structure Alert	Stage	Acceptance Criteria and where monitored or controlled
BB	1-Bromo-Butyne		Starting material-Stage I-Preparation of BBQX-6	LT 30ppm (DL)/ Drug substance supplier analysis for five BBQX intermediate batches
BBQX-7	2-chloromethyl-4-methyl-Quinazoline		Starting material-Stage II-Preparation of BBQX	LT 30ppm (DL)/ Drug substance supplier analysis for three batches

Recommendation for Module 2

- **DS Retest date: NMT 12 months unless conduct in-house Stability tests.**
- **Reference Standards for DS and DP:**
  - **If characterization report not from DP manufacturer: applicant still needs to interpret all spectral data to confirm all structures**
  - **If you have used USP reference standard, IR comparison is sufficient**

Analytical Test Methods and Validation

- **Verification highly recommended for compendial procedures - refer to USP <1226>**
- **Verification highly recommended for method transfer from DMF holder/outside lab to ANDA sponsor- refer to USP<1224>**
- **Full validation reports highly recommended for in-house methods-refer to USP<1225>**
- **Equivalency data to show that in-house method is equivalent to or better than the USP method- refer to USP<1225>**

Analytical Test Methods

Chromatographic Conditions

Mobile Phase			
Diluent			
Column			
Detector			
Flow Rate			
Injection Volume			
Wavelength			
Column Temp.			
Gradient program	Time in min	%Mobile phase A	%Mobile phase B
Run time			
Sample and Standard Preparation			
System Suitability			

Validation Summary

Parameter	Results
Precision: System repeatability	
Precision: Method repeatability	
Specificity	
Detection Limit	
Quantitation Limit	
Linearity	
Accuracy a) Deviation from linearity	
Accuracy: b) Recovery of impurities	
Range	
Robustness	
Stability of standard solutions	
Stability of sample solutions	

Module 3 – Quality

1. 3.2.S. Drug Substance
2. 3.2.P. Drug Product
3. Appendices (Agents Safety Evaluation)
4. 3.2.R. Regional Information
5. Literature References

❖ Follow the instruction in "Guidance for Industry (DRAFT) ANDA Submissions - Content and Format of Abbreviated New Drug Applications (June 2014)

Summary

- **Applicant should show an understanding of The principles, materials, technology and potential sources of variation.**
- **Provide complete, well written & organized documents**
- **Proofread to avoid discrepancies between Modules 2 & 3**
- **Quality Overall Summary (QOS) or Module 2 should include a summary of Module 3**

Take Away

Increase the probability of "right- first-time" submission

Deliver a high quality product that meets patient needs

Acknowledgements

Thanks to:

- **Susan Rosencrance**
- **Peter Capella**
- **Geoffrey Wu**
- **Damaris Maldonado**

References & Resources

OPQ Questions

CDER-OPQ-Inquiries@fda.hhs.gov

Common Technical Document (CTD)

e-CTD Questions

esub@fda.hhs.gov

- MaPP 5015.10: Chemistry Review of Question-based Review (QbR) Submissions
- ICH M4Q: The CTD - Quality
- Guidance for Industry (DRAFT) ANDA Submissions - Content and Format of Abbreviated New Drug Applications

Thank you for your attention!

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