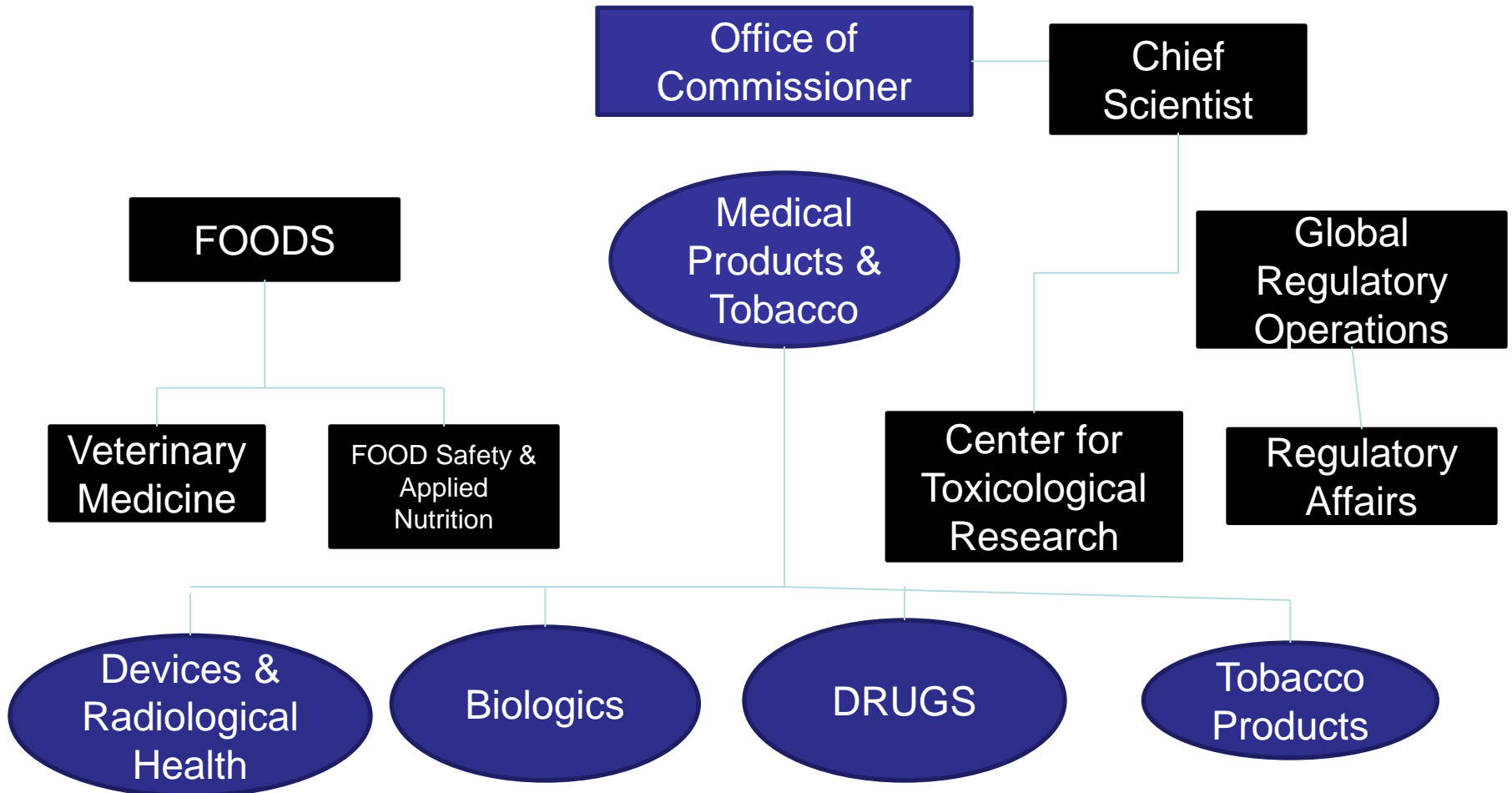


How to Avoid **Common** **Deficiencies in INDs and** **NDA**s

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Structure of FDA



Structure of CDER

13 Offices and to name a few below:

- Office of New Drugs
- Office of Pharmaceutical Sciences
- Office of Clinical Pharmacology
- Office of Translational Sciences
- Office of Medical Policy
- Office of Compliance
- Office of Surveillance and Epidemiology

Drug Approval Process- Overview

- **Discovery**
- **Development-
Chemistry/Biology/Feasibility**
- **Non-Clinical**
- **Pre- IND**
- **IND- Phase I**

Drug Approval Process- Overview (cont.)

- IND- Phase II
- IND-Phase III
- NDA Submission to FDA for Approval
- Phase IV-Post Marketing Surveillance

Time Lines

- Investigational New Drugs- Phase I
 - 30 days
- NDA
 - Standard 10 months
 - Priority- 6 months
- Supplemental applications
 - Prior Approval (4 months)
 - CBE-30 (6 months)

Importance of Chemistry



What is a Deficiency?

- Inadequate or incomplete scientific information submitted in an application that prevents a reviewer from making a well informed regulatory decision.

Content

- CMC Essentials of any application
(21 CFR 314.50)
 - INDs
 - NDAs
 - Supplemental NDAs
- Organization of a submission
 - eCTD format

CMC **Essentials**- IND

(for an approved Drug Product)

- Information Required On
 - Drug Substance
 - Drug Product
 - Packaging and Stability (if manipulated)
 - Placebo Information
 - Labeling

Drug Substance-API

- Chemistry
 - Molecular Structure and Analysis
 - Physical and Chemical Properties
 - Pharmacological Basis of Drug Action
 - Synthetic Route
 - Purification Methods
 - Purity and Impurities
 - Stability

Drug Product

- Dosage Form
- Inactive Ingredients
- Components and Composition
- Formulation
- Manufacturing process
 - In-process control strategy
- Packaging
- Stability
- Labeling

eCTD - 3.2: Body Of Data

- **S** **DRUG SUBSTANCE [Name, Manufacturer]**
- **S.1** **General Information [name, manufacturer]**
- **S.1.1** ***Nomenclature***
- **S.1.2** ***Structure***
- **S 1.3** ***General Properties***

Drug Substance (cont.)

- **S.2 Manufacture [name, manufacturer]**
- **S.2.1** *Manufacturers*
- **S.2.2** *Description of Manufacturing Process and Process Controls*
- **S.2.3** *Control of Materials*
- **S.2.4** *Controls of Critical Steps and Intermediates*
- **S.2.5** *Process Validation and/or Evaluation*
- **S.2.6** *Manufacturing Process Development*

Drug Substance (cont.)

- **S.3** **Characterization [name, manufacturer]**
- **S.3.1** ***Elucidation of Structure and other Characteristics***
- **S.3.2** ***Impurities***
- **S.4** **Control of Drug Substance [name, manufacturer]**
- **S.4.1** ***Specification***
- **S.4.2** ***Analytical Procedures***
- **S.4.3** ***Validation of Analytical Procedures***
- **S.4.4** ***Batch Analyses***
- **S.4.5** ***Justification of Specification***

Drug Substance (cont.)

- **S.5** **Reference Standards or Materials [name, manufacturer]**
- **S.6** **Container Closure System [name, manufacturer]**
- **S.7** **Stability [name, manufacturer]**
- **S.7.1** ***Stability Summary and Conclusions***
- **S.7.2** ***Postapproval Stability Protocol and Stability Commitment***
- **S 7.3** ***Stability Data***

Drug Product

- **P** **DRUG PRODUCT [Name, Dosage form]**
- **P.1** **Description and Composition of the Drug Product [name, dosage form]**
- **P.2** **Pharmaceutical Development [name, dosage form]**
- ***P.2.1*** ***Components of the Drug Product***

Drug Product (cont.)

- ***P.2.1.1*** ***Drug Substance***
- ***P.2.1.2*** ***Excipients***
- ***P.2.2*** ***Drug Product***
- ***P.2.2.1*** ***Formulation Development***
- ***P.2.2.2*** ***Overages***
- ***P.2.2.3*** ***Physicochemical and Biological Properties***
- ***P.2.3*** ***Manufacturing Process Development***

Drug Product (cont.)

- ***P.2.4*** ***Container Closure System***
- ***P.2.5*** ***Microbiological Attributes***
- ***P.2.6*** ***Compatibility***
- ***P.3*** ***Manufacture [name, dosage form]***
- ***P.3.1*** ***Manufacturers***
- ***P.3.2*** ***Batch Formula***

Drug Product (cont.)

- **P.3.3** *Description of Manufacturing Process and Process Controls*
- **P.3.4** *Controls of Critical Steps and Intermediates*
- **P.3.5** *Process Validation and/or Evaluation*

Drug Product (cont.)

- **P.4** **Control of Excipients [name, dosage form]**
- ***P.4.1*** ***Specifications [name, dosage form]***
- ***P.4.2*** ***Analytical Procedures***
- ***P.4.3*** ***Validation of Analytical Procedures***
- ***P.4.4*** ***Justification of Specifications***
- ***P.4.5*** ***Excipients of Human or Animal Origin***
- ***P.4.6*** ***Novel Excipients***

Drug Product (cont.)

- **P.5** **Control of Drug Product [name, dosage form]**
- ***P.5.1*** ***Specification(s)***
- ***P.5.2*** ***Analytical Procedures***
- ***P.5.3*** ***Validation of Analytical Procedures***
- ***P.5.4*** ***Batch Analyses***
- ***P.5.5*** ***Characterization of Impurities***
- ***P.5.6*** ***Justification of Specification(s)***

Drug Product (cont.)

- **P.6** **Reference Standards or Materials [name, dosage form]**
- **P.7** **Container Closure System [name, dosage form]**
- **P.8** **Stability [name, dosage form]**
- ***P.8.1*** ***Stability Summary and Conclusion***
- ***P.8.2*** ***Postapproval Stability Protocol and Stability Commitment***
- ***P.8.3*** ***Stability Data***

APPENDICES

- **A.1** **Facilities and Equipment (biotech only)**
- **A.2** **Adventitious Agents Safety Evaluation**
- **A.3** **Novel Excipients**

REGIONAL INFORMATION

- **R1** **Executed Batch Records**
- **R2** **Comparability Protocols**
- **R3** **Methods Validation Package**

Other Information

- **Review Of Common Technical Document-Quality (Ctd-Q) Module 1**
 - **A. Labeling & Package Insert**
 - **B. Environmental Assessment Or Claim Of Categorical Exclusion**

Some Common CMC Filing Deficiencies

- Inadequate information in a eCTD submission
- e.g.
 - In-process Controls
 - Justification for Regulatory Specifications
 - Sterility Validation (if parenteral)
 - Incomplete Stability information

Filing Deficiencies- Impact

- **IND**- Generally goes on 'Clinical Hold'
- **NDA**- Inadequate information - may not be filed (depending upon the risk factor)
- **Supplemental NDA**- Generally filed and may end up with a 'Complete Response' with deficiencies or 'Information request' during review cycle

Examples of Dosage Specific Deficiencies

- **Transdermal Patches:**
 - Manufacturing Process
 - Specifications of the final drug product (Adhesive force/adhesivity and Tack)
 - Stability Information (cold flow, crystal formation)

Examples of Dosage Specific Deficiencies

- Metered Dose Inhalers (Aerosols):
 - Delivered Dose
 - Extractables and Leachables
 - Plume Geometry
 - Particle Size Distribution

Examples of Dosage Specific Deficiencies

- Parenteral drugs & device combinations (e.g. prefilled syringes)
 - Extractables and Leachables
 - Sterility
 - Validation of Sterility
 - Stability
 - Particulates
 - Microbial Effectiveness Tests
 - Delivered Dose

Examples of Dosage Specific Deficiencies

- Extended Release Tablets/ Capsules / Chewable Tablets etc.:
 - Formulation Development
 - Dissolution Specifications

Discussion with an Example-1

- Applicant 'A' changes the process of an approved drug product by changing the size of all equipments to manufacture a larger scale for one of their chewable tablets product. Provides with comparative dissolution testing data for the two marketed strengths in only one medium between the approved scale and the proposed scaled up batches.

Deficiency or Information Request?

- No deficiency
- Request for more information asking the applicant to provide comparative dissolution in two additional media for the equipment change.
- Request the applicant to provide comparative dissolution information in 5 media for each strength for the equipment change associated with the batch size and f_2 data in pH 5 media that are needed to support the equipment changes.

Discussion with an Example-2

- Applicant 'B' submits an NDA for their new molecular drug 'chilledon'. The application appears to be complete on the face. This injection product does not have sterility validation information in their submission. The facility information for the drug substance and drug product is incomplete. The stability data included for six months real time and accelerated data for DS and DP.

Deficiency

- Not filable due to incomplete submission
- Application will be filed but these information will be requested in the 75 day filing letter, if there is a demonstrated clinical advancement
- The project manager calls the applicant and begs the applicant to send these data so that this can be filed.

Discussion with an Example-3

- Applicant 'C' filed an amendment to their NDA currently under review in the Agency, to change their analytical methods for their new molecular entity drug product. In the process their specifications are also changed to represent the proposed analytical methodology.

Discussion with an Example-3

- No validation data
- No raw data
- No justification for changing the specifications
- Incomplete submission

What else do you think is another missing link here?

Discussion with an Example-4

- Applicant 'D' files for an Investigational New Drug (IND) application which was allowed to proceed. After one year into their phase II trials, they send an amendment to the IND to change the drug substance manufacturer because they could not continue with the current manufacturer due to some contractual misunderstanding. How does it affect the NDA review? Consequences?

Some Packaging Deficiencies

- Stability of the drug product is packaging dependent invariably in all cases.
 - Moisture ingress
 - Oxygen ingress
 - Extractables and Leachables
 - Moisture absorbents
 - Material changes after approval

References to Guidance's

- Guidance for Industry: *Content and Format of Investigational New Drug Applications (INDs) Including Well-Characterized, Therapeutic, Biotechnology-derived Products***
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071597.pdf>
- Guidance for Industry: *INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information***
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070567.pdf> and the 21 CFR 312.23.

References

- **Guidance for Industry: Q3A (R) Impurities in New Drug Substances**
- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf>.
- **Guidance for Industry: Q3B (R2) Impurities in New Drug Products**
- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf>

References

- **Guidance for Industry: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances***
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm134966.htm>
- **Guidance for Industry: *Container Closure Systems for Packaging Human Drugs and Biologics Chemistry, Manufacturing and Controls Documentation***
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070551.pdf>

References

- **Guidance for Industry: *Q2A Text on Validation of Analytical Procedures***
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073381.pdf>.
- **ICH guidance for industry, *Q2B Validation of Analytical Procedures: Methodology*, available at**
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073384.pdf>.
- **Guidance for Industry: *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches***
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf>



Additional Information

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