U.S. FOOD & DRUG ADMINISTRATION

CMC Insights to Formulating a NDA

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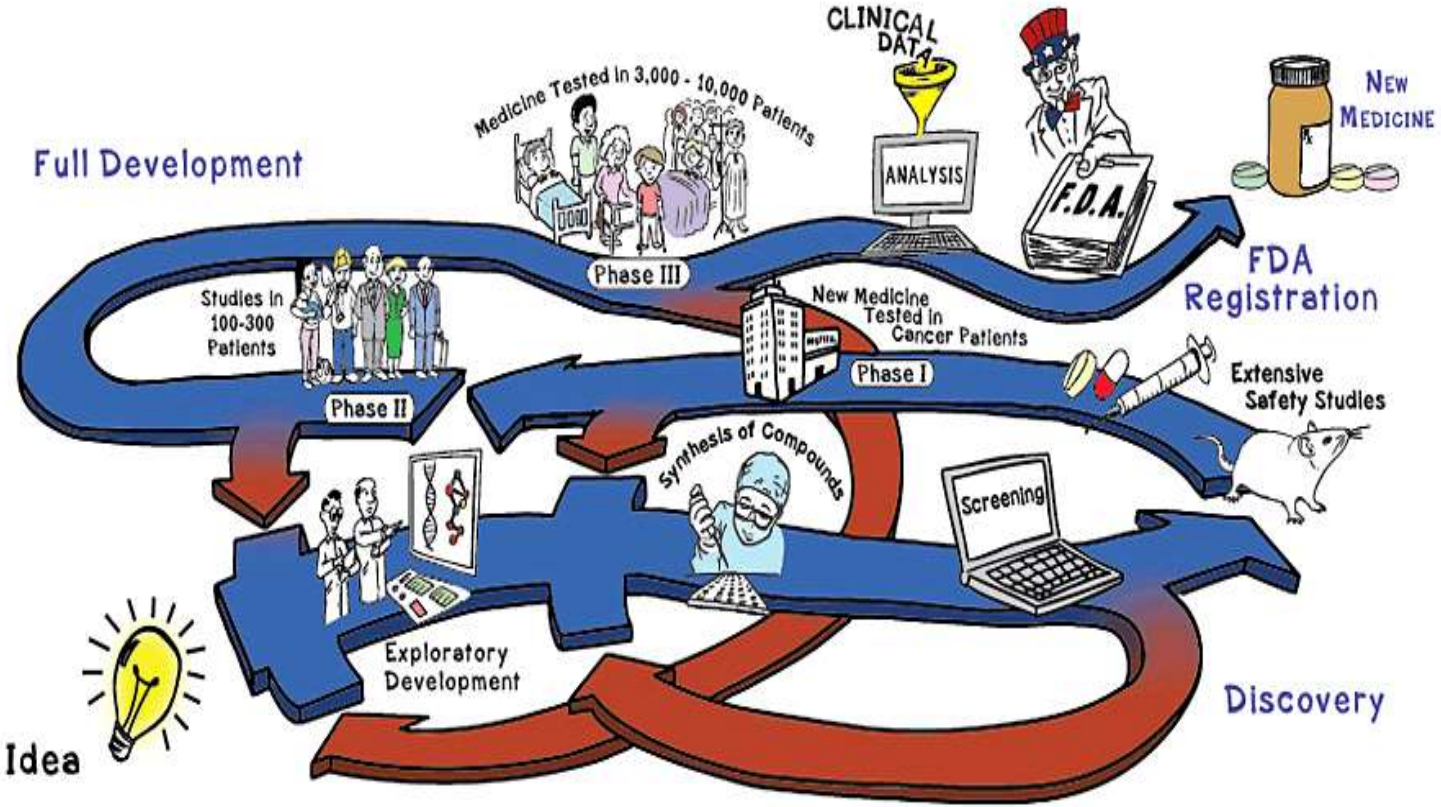
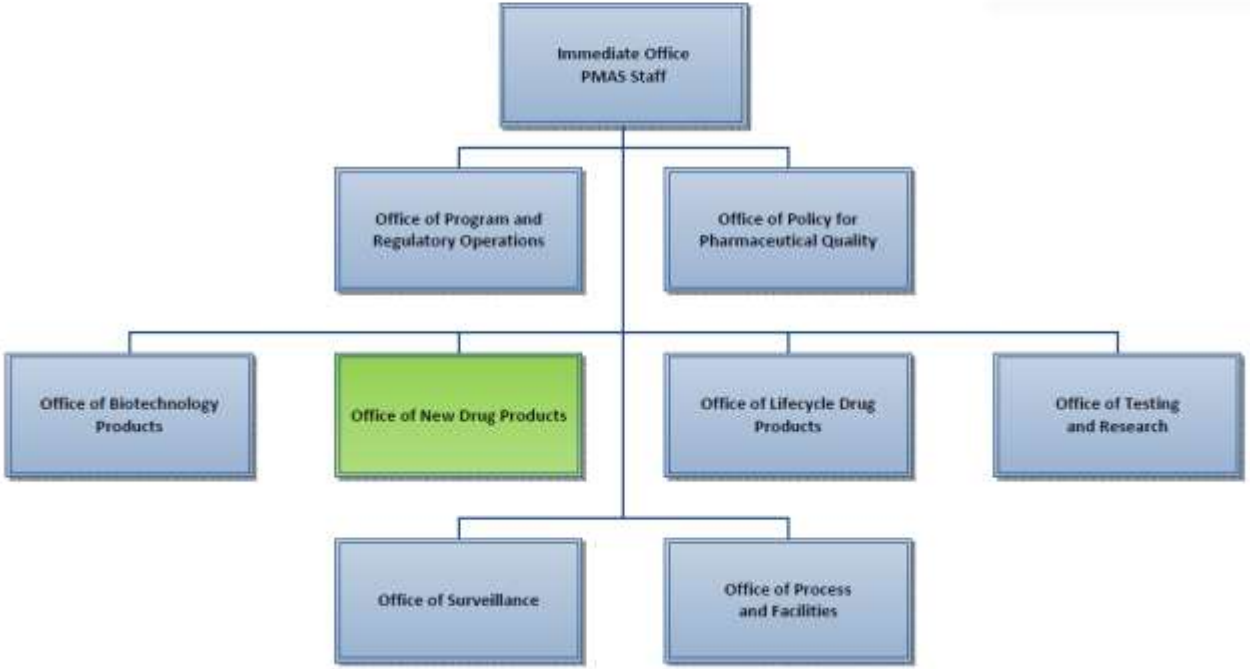

Full Development
Medicine Tested in 3,000 - 10,000 Patients
CLINICAL DATA
ANALYSIS
F.D.A.
NEW MEDICINE
FDA Registration
Phase III
Studies in 100-300 Patients
New Medicine Tested in Cancer Patients
Phase I
Extensive Safety Studies
Phase II
Synthesis of Compounds
Screening
Exploratory Development
Discovery
Idea

Presentation Outline

- Office of Pharmaceutical Quality Structure
- NDA structure & Content
- Quality Expectations and Importance
- NDA Filing and Review Issues
- Case Studies
- Conclusions

THE OFFICE OF PHARMACEUTICAL QUALITY



Office of Pharmaceutical Quality

- Combines components of previous CDER Office of Pharmaceutical Sciences and CDER Office of Compliance
- Intended to provide better alignment between all quality functions (review, inspection, research)
- Focus areas for the new office:
  - Integrated approaches for review and inspection
  - Risk based approaches to review and inspection
  - Efficiency and risk-based work prioritization
  - Modern regulatory science approaches

What is Pharmaceutical Quality?

- The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as identity, strength and purity (ICH Q6A)

- The degree to which a set of inherent properties of a product, system or process fulfills requirements (ICH Q9)

Patient & Product

Product & Process

Expectations for Quality

- Patients and caregivers assume that their drugs:
  - Safe and efficacious
  - Deliver the same performance as described in the label
  - Perform consistently over their shelf life
  - Are made in a manner that ensures quality
  - Will be available when needed

➢ *Quality expectations are not based on the approval process (accelerated vs. regular)*

Quality Considerations: IND Stage

- Starts at IND/Pre-NDA stage
  - Start thinking about product development strategies at IND stage
  - Focus on clinical/commercial product comparability
    - Discuss strategy and data required with FDA
  - Stability data package to be submitted
    - Need for proposed stability amendments
    - Available supporting stability data
  - Commercial manufacturing sites information
    - Will sites be ready for inspection

Critical Quality Attributes

How familiar are you with Critical Quality Attributes?

a) Very familiar

b) Somewhat familiar

c) Not familiar

Critical Quality Attributes

- "A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality"

  - ICH Q8 (R2)

CDER Regulatory Submissions

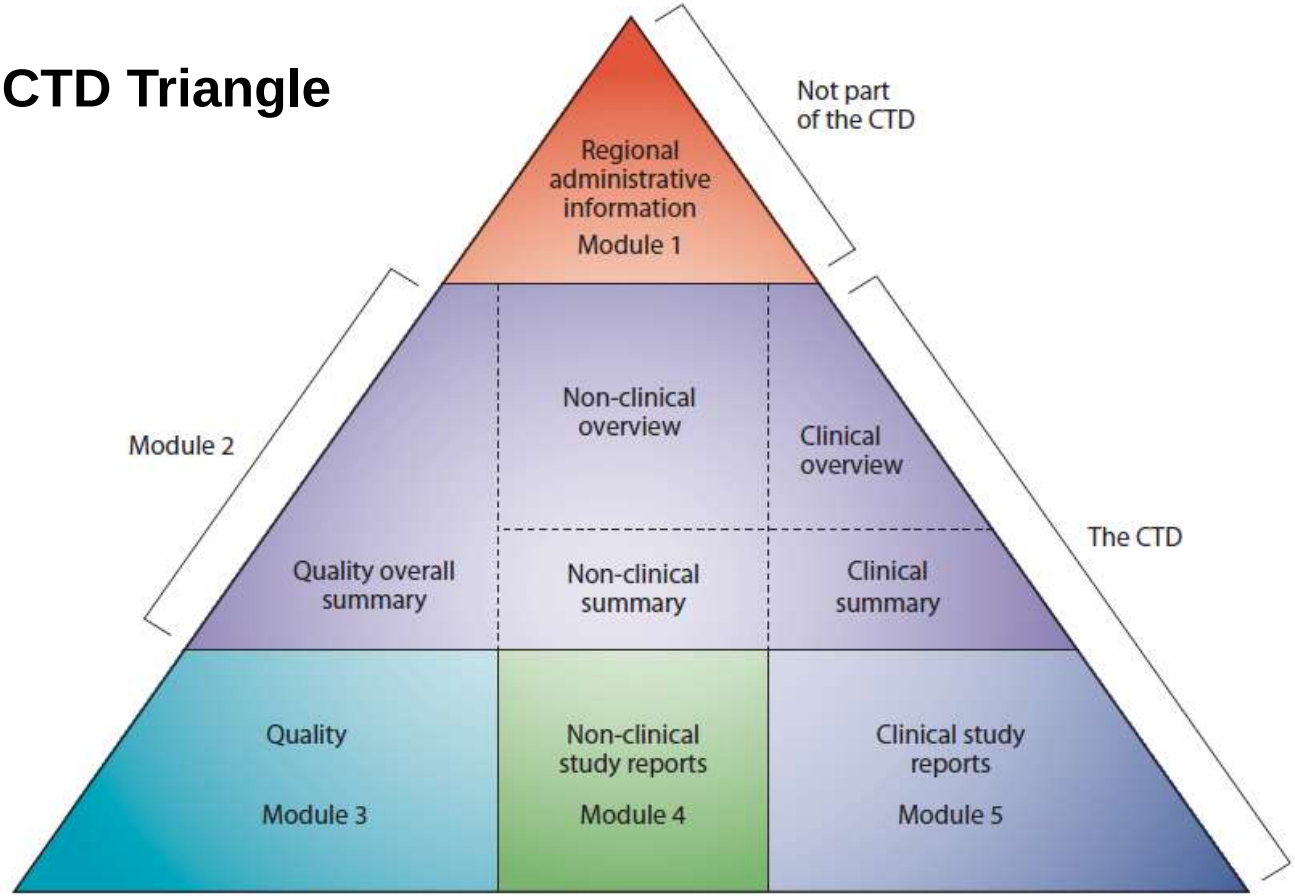
Investigational New Drugs (INDs)
- Initial INDs (Research/commercial)
- Amendments
- Special Protocol Assessments (SPAs)

New Drug Applications (NDAs)
- Original NDA submissions
- Commitments/protocols
- Supplements
- Annual Reports

Drug Master Files (Types I, II, III, IV, and V)

Content and Format of an NDA
21 CFR 314.50

CTD Triangle

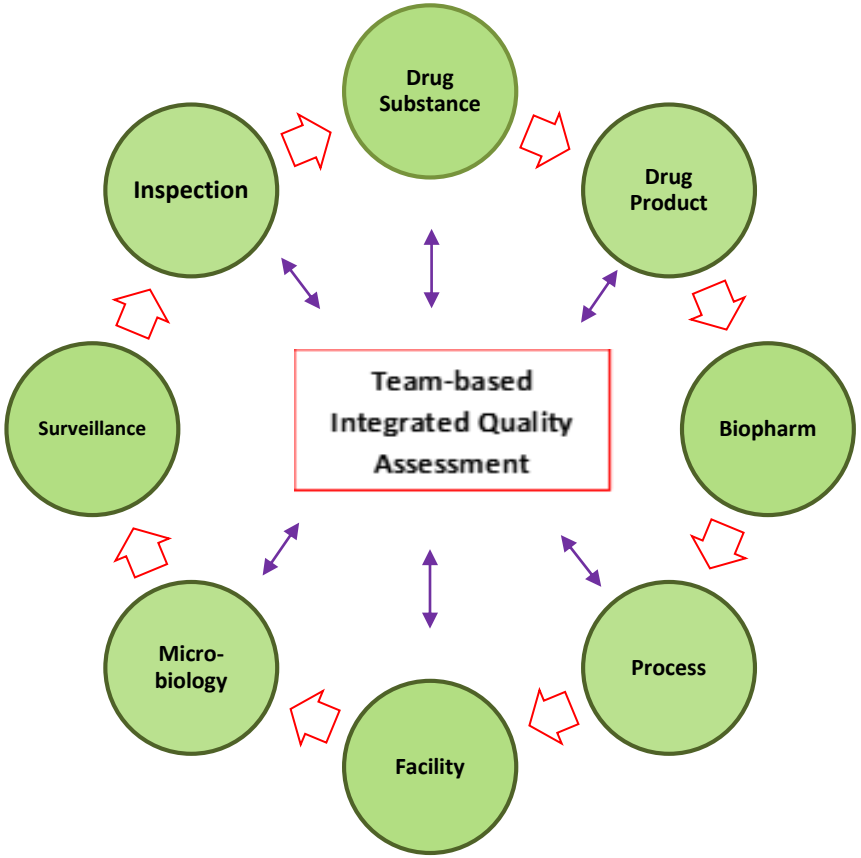


The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

Filing

- Upon NDA receipt, Integrated Quality Assessment (IQA) team assesses NDA for filability
  - Application Technical Lead (ATL), drug substance, drug product, process, biopharmaceutics and facility reviewers
  - Product Quality Microbiology Reviewer, (or others) as needed
- Filability recommendation conveyed to clinical division in which new NDA resides
- Official Refuse to File determination (clinical)

OPQ Product Quality Review Team



CMC Information

- **Drug Substance**

- Physical & Chemical Characteristics – Polymorphs
- Manufacturer Name and Address – Ready for Inspection
- Synthesis and Controls – Starting Materials – ICH Q11
- Analytical Methods
- Specification – ICH Q6A
- Impurities – ICH Q3 A (R2)
- Stability – ICH Q1A (R2)

CMC Information

- **Drug Product**

- Physical & Chemical Characteristics – Polymorphs/Particle size
- Manufacturer Name and Address – Ready for Inspection
- Components and Composition
- Manufacturing and Packaging
- Master Production Record (21 CFR § 314.420)
- Specification - ICH Q6A
- Stability - ICH Q1A (R2)
- Post-Approval Commitment

An Example of a Drug Substance Specification

Test	Analytical Procedure	Acceptance Criteria
Appearance	Visual	Color, powder
Identity	IR or HPLC/UV	Matches Standard
Assay	HPLC	90-110%
Impurities (specified, unspecified and total)	HPLC	NMT # %
Water	KF	NMT # %
Residual Solvents	GC	USP <467>
Residue on Ignition	In-House Method	≤ # w/w
Particle Size	In-House Method	D10 ≥ # µm D50 ≤ # µm D90 ≤ # µm
Microbial Limits	USP	NMT # cfu/g; absence of pathogenic organisms;

An Example of a Drug Product Specification

Attribute	Analytical Procedure	Acceptance Criteria
Identity	IR or HPLC/UV	Matches Standard
Appearance	Visual	Color, Imprint
Assay	90-110%	HPLC
Impurities (Related substances)	<1% to few %	HPLC
Release from Dosage form	80% in 15 minutes	Stirred vessel
Dose Uniformity	HPLC or Weight	Statistical Criterion (USP)
Particulate Matter	USP	NMT #
Water Content	Chemical or weight loss	Few %
Microbial Limits or sterility	USP	NMT # cfu/g; absence of pathogenic organisms; Sterile
Bacterial Endotoxins	USP	NMT #
Reconstitution Time	IHM	NMT # seconds

Poll!

At the time of NDA submission, form 356h should:

a) List all facilities

b) List only key facilities

c) Indicate being ready for inspection

d) List and indicate being ready for inspection

Top Ten Review Issues

- Extractables and leachables
- In-use studies to support label recommendations (storage time/duration)
- Compatibility to co-administered drugs
- Dissolution method
- Salt Policy
- Polymorph control/testing
- Characterization of impurities
- Stability indicating methods not adequately validated
- Non-functional score/Insignia/Identifier
- Miscellaneous

Case Study: Leachables

- IV for treating bacterial infection
- Extractables & Leachables on primary packaging and Infusion sets (IS)
- Leachables from select IS above TTC identified
- Restricted for use with select IS
- Label identifies compatible IS

Manufacturing Challenges

- The manufacturing process must be sufficiently developed to support the CMC section
- Sites must be ready for inspection at the time of submission
- Application must meet same standards as other applications to support approval
- Sponsor and Manufacturers must demonstrate that the commercial process is ready to be implemented in conformance with cGMP

Case Study: Facilitating Facilities Conversation

- SODF for a Transplant indication
- Applicant identified several facilities for Drug Substance and Drug Product manufacturing/testing in the pre-submission meeting package.
- CMO appeared not be in compliance with GMP
- Applicant seemed to be unaware of the status
- IR comment to Applicant triggered communication between the CMO and the Applicant.

Quality Considerations: Manufacturing

- Set yourself up for success:
  - Generate process and product knowledge to demonstrate manufacturing process is viable
  - Plan for the unexpected (facility qualification failures, manufacturing schedules)
  - Communicate issues between sponsors and contract manufacturers

Quality Considerations: Manufacturing

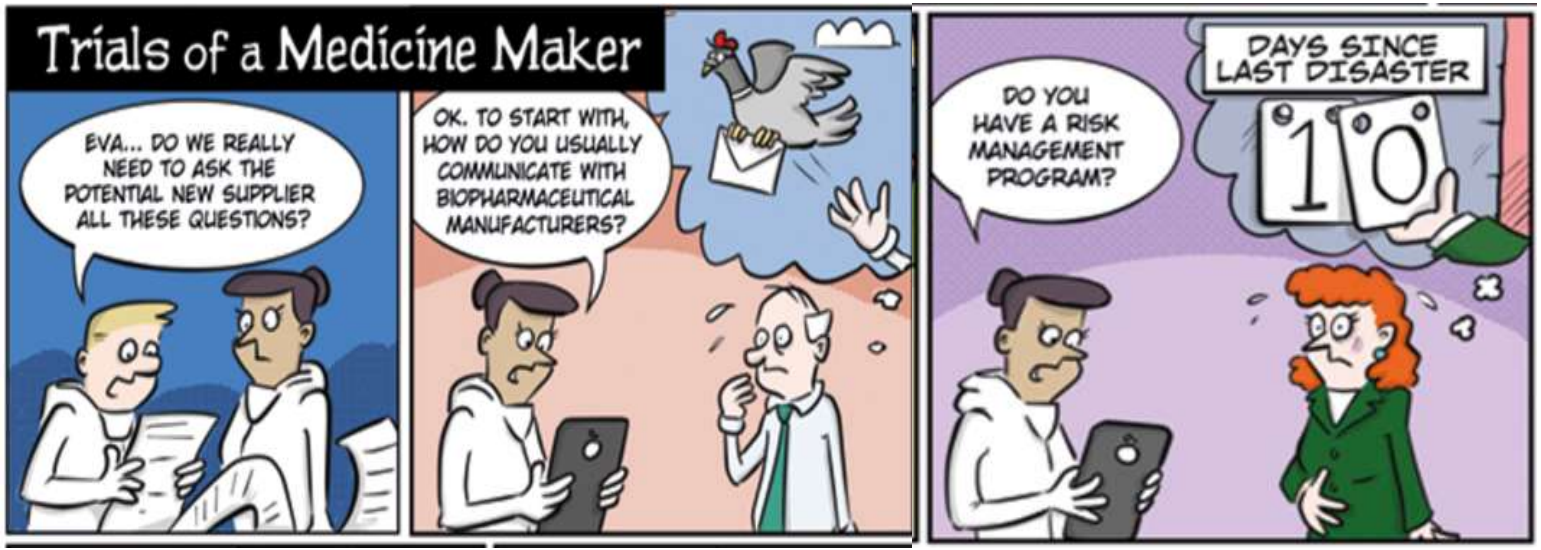
- Set yourself up for success:
  - Resolve manufacturing issues in a timely manner (quick and comprehensive response)
  - Pursue effective discussions with the FDA
  - Provide transparent design evolution and rationale for the commercial manufacturing process and controls

Case Study: Lack of Communication

- Small volume parenteral for cancer
- Applicant employed 2 API intermediate manufacturers and 1 final API manufacturer
- Final API manufacturer observed particulates in material received from 1 of the 2 intermediate sites and notified the Applicant
- Applicant did not convey findings to the implicated intermediate facility OR the sister facility
- Withdrew the site to facilitate further evaluation

Case Study : Early Communication!

- SODF for Cancer
- Sponsor made final decisions on dosage form, manufacturing process and controls in anticipation of BTT designation
- Issue with finished manufacturing process affecting specifications
- Proactively met early to discuss issues before filing
- Sponsor discussed the failure, investigation and corrective actions
- Involved multiple agency review disciplines to evaluate and provide feedback
- Sponsor discussed path forward, and impact to CMC data
- Facilitated review and provided agency with clearer understanding during review process


Trials of a Medicine Maker
EVA... DO WE REALLY NEED TO ASK THE POTENTIAL NEW SUPPLIER ALL THESE QUESTIONS?
OK. TO START WITH, HOW DO YOU USUALLY COMMUNICATE WITH BIOPHARMACEUTICAL MANUFACTURERS?
DO YOU HAVE A RISK MANAGEMENT PROGRAM?
DAYS SINCE LAST DISASTER
10

Case Study: Compatibility

- IV formulation indicated for cancer
- Sponsor developed a new formulation of an approved product – 505(b)(2)
- Label listed co-administered drug as for the Listed Drug (LD)
- Testing revealed incompatibility with certain drugs
- Removed incompatible drugs from the label

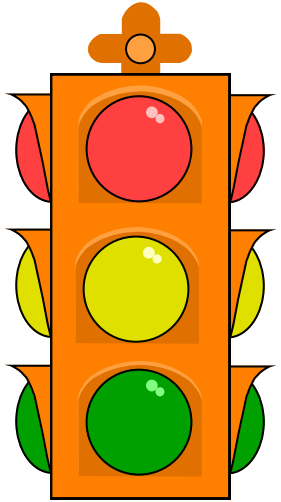
Examples of Potential Quality RTF Issues

- Undefined manufacturing facilities and/or lack of confirmation of facility information
- Insufficient stability data to support a commercially viable expiration date
- Significant changes to the commercial formulation following clinical trials
- Insufficient parallel between primary stability batches and proposed commercial formulation(s)

NDA Actions

Approval

Complete Response



Conclusions

- Ensure CMC information provided will support the identity, quality, purity and strength
- Early discussion; stay engaged
- Quick turn-around time for information requests
- Availability for quick teleconference
- Discussion of residual product quality risk and appropriate mitigation strategies
- Discussion of launch challenges, if any

Thank you!

U.S. FOOD & DRUG ADMINISTRATION

Common Pitfalls of Biologics License Applications (BLAs)

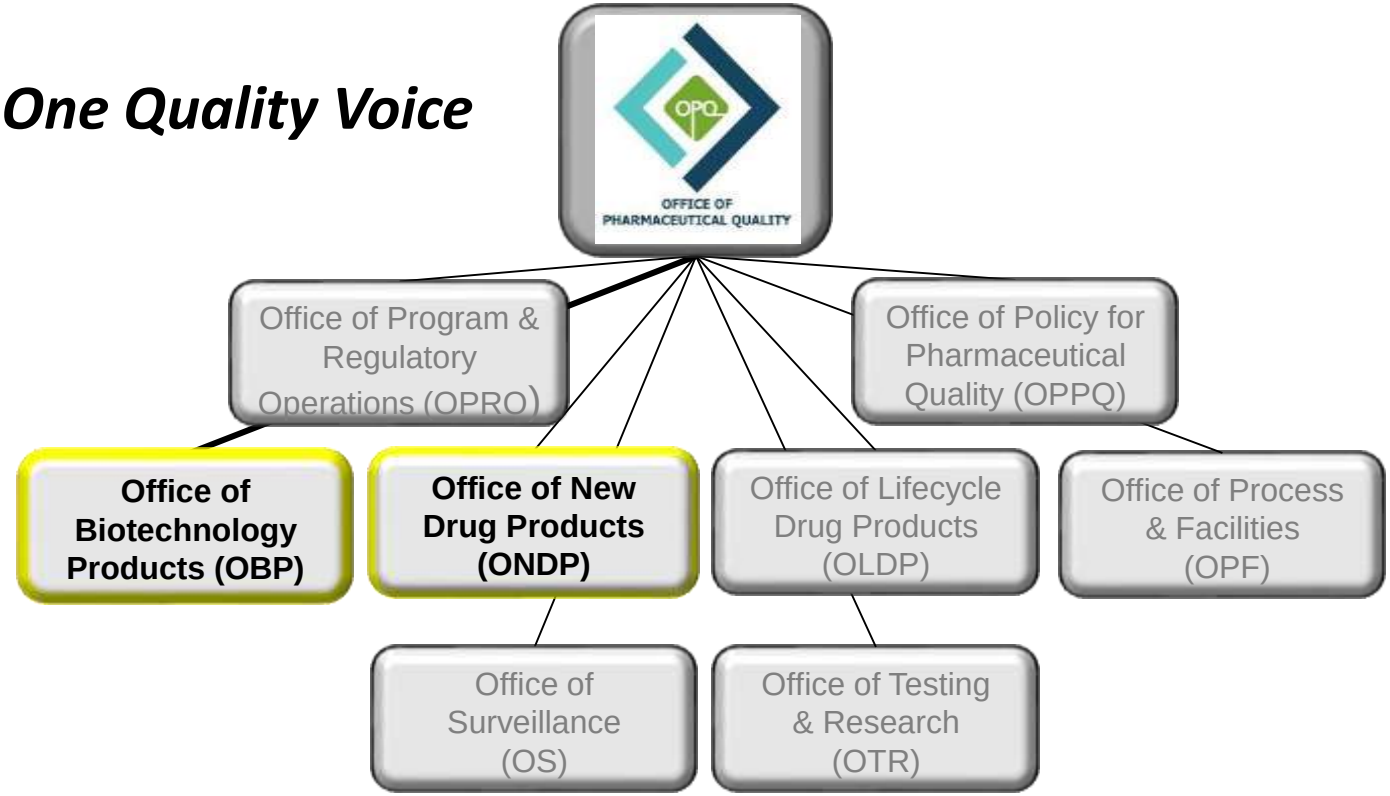
Steven Bowen Ph.D.
Chemist
Office of Biotechnology Products
CDER

Presentation outline

- Structure of the Office of Pharmaceutical Quality
- Relevance of the CMC information
- Differences between small molecules and biologics
- BLA review process
- Common problem areas resulting in IRs, PMCs, CRs

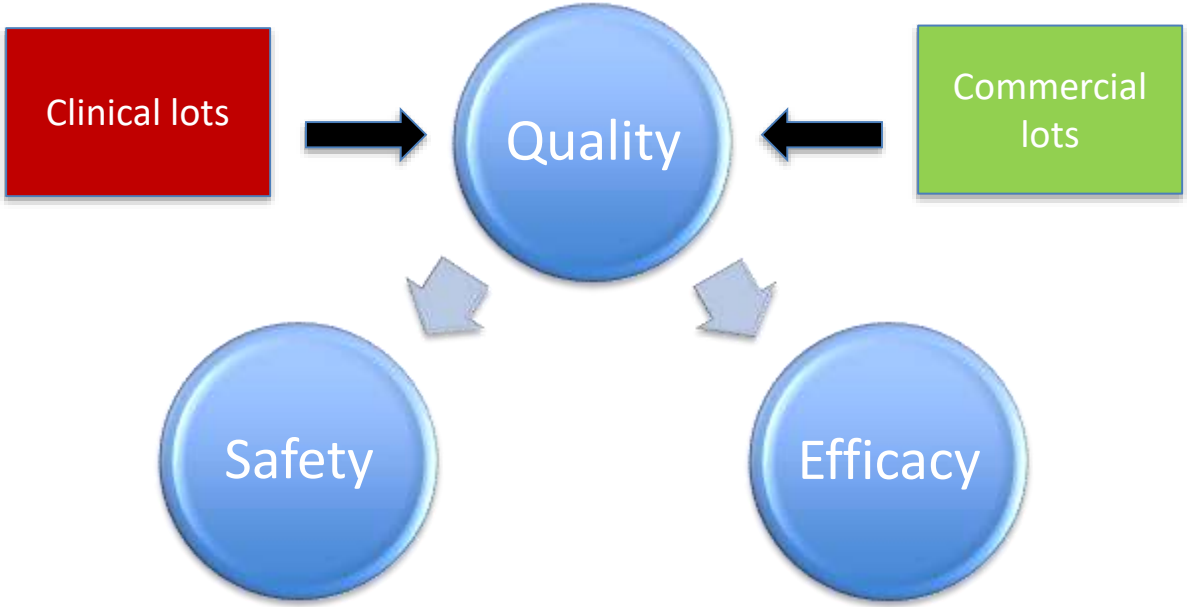
Office of Pharmaceutical Quality

One Quality Voice



The Office of Pharmaceutical Quality assures that quality medicines are available for the American public.

Product Quality



Manufacture of a product of consistent quality assures the clinical performance of commercial lots with regards to safety and efficacy to be the same as the clinical lots

Small molecules vs Biologics

Small molecules

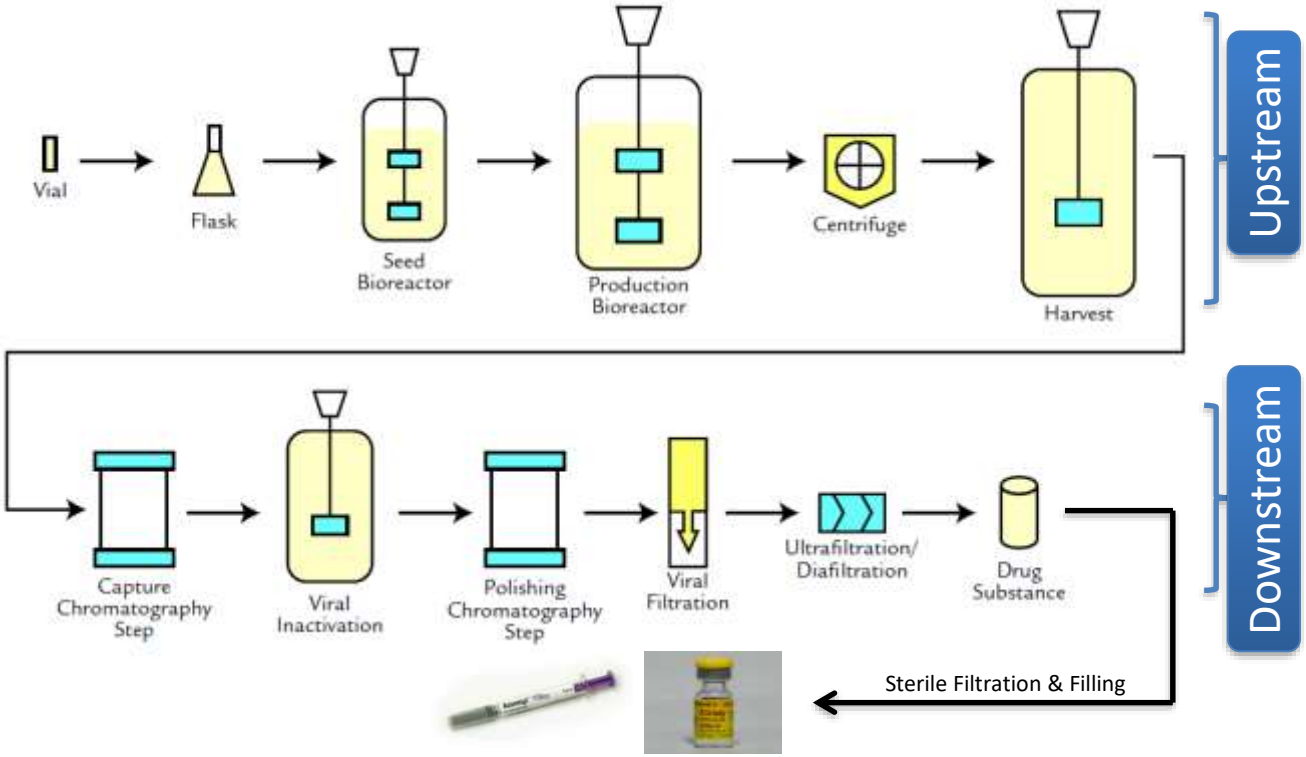
- <900 daltons
- Chemical synthesis
- Semi-synthetics
- Well defined structures
- Regulated under the FD&C
- Purity, safety and strength
- New Drug Application (NDA)
- Reviewed in ONDP

Biologics regulated in CDER*

- Protein > 40 amino acids
- Produced in a living system
- Complex structures
- Regulated under FD&C and PHS Act
- Purity, safety and potency
- Biologics License Application (BLA)
- Reviewed in OBP

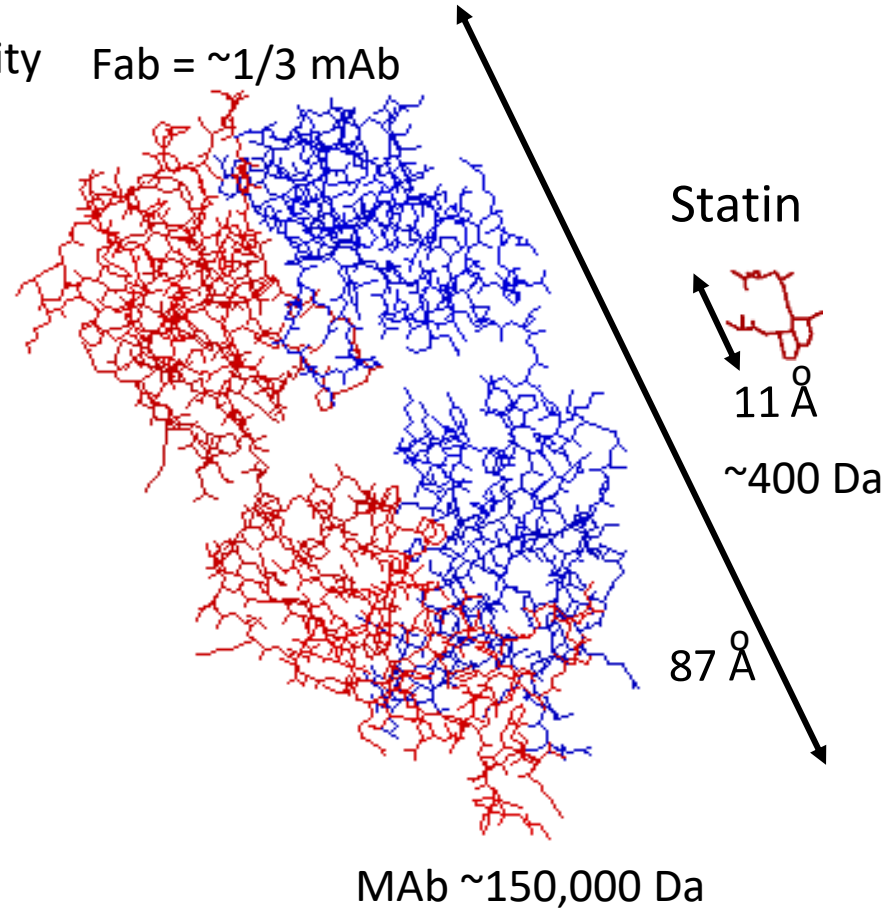
*For a complete definition of a biological product see 21 CFR 600.3(h)

Biologics Manufacturing Process



Small molecules vs Biologics

- Size and heterogeneity
- Tertiary structure critical for biological activity
- Sensitive to small changes in manufacturing
- Complex manufacturing processes
- Ability to transmit infectious agents
- Potency
- Immunogenicity



Examples of Drugs and Biologics

ONDP Products

- Fermentation products
- Small molecules
- Peptides
- Complex mixtures (heparins)
- Oligonucleotides
- Hormones
- Antibody Drug Conjugates

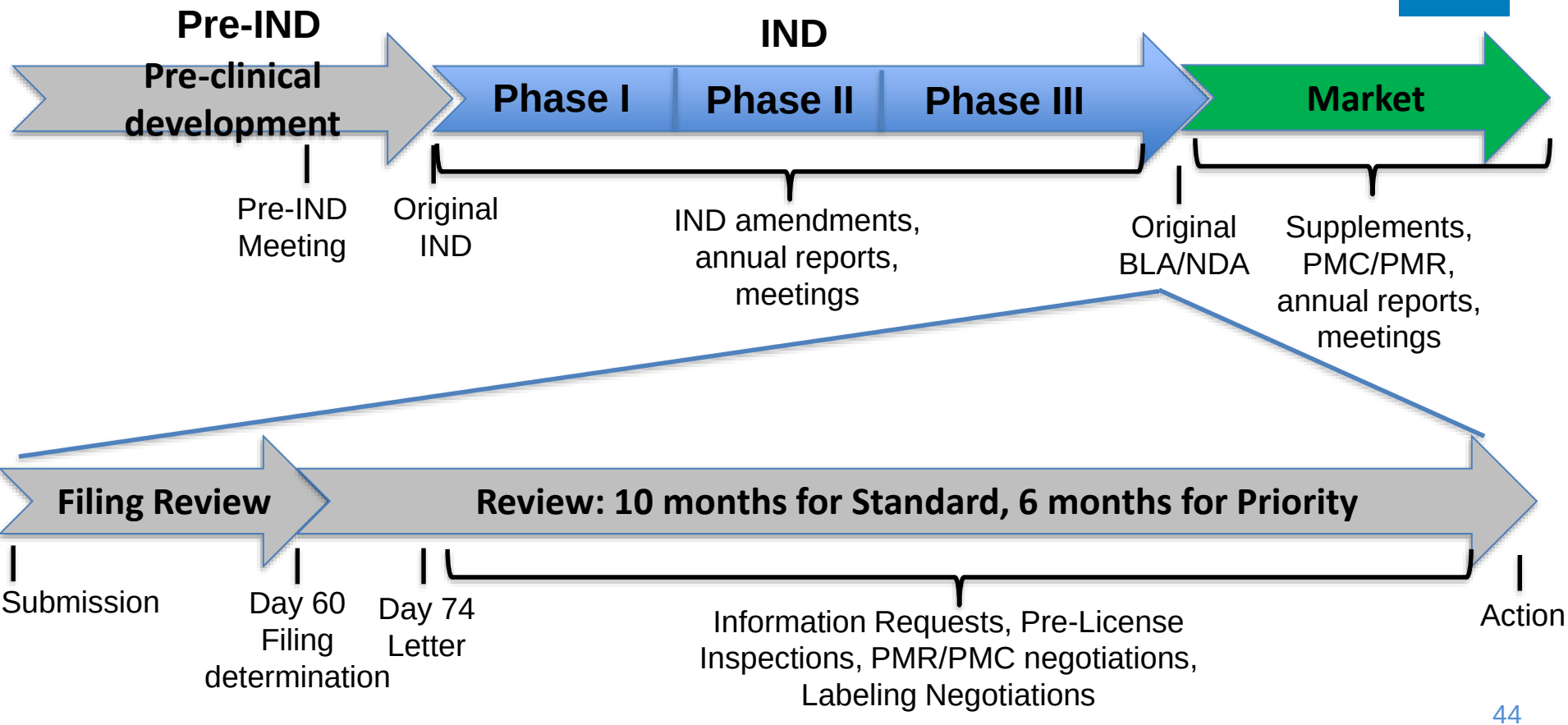
OBP Products

- Monoclonal Antibodies
- Enzymes
- Growth Factors
- Cytokines
- Toxins
- Fc and Fab Fusion Proteins
- Antibody Drug Conjugates
- Biosimilars
- Transition products

Transition Products

- BPCI Act (2009):
  - Biological products approved under section 505 of the FD&C Act (NDA) will be deemed as a license (BLA) under section 351 of PHS Act
  - Transition products (e.g. insulins, reproductive hormones) will be regulated by OBP as BLAs as of March 23, 2020
  - FDA Guidance:
    - *Interpretation of the "Deemed to be a License" Provision of the BPCI Act of 2009*, December 2018
    - *Interpretation of the "Deemed to be a License" Provision of the BPCI Act of 2009: Questions and Answers*, December 2018

Biologic Product Lifecycle



OPQ Review Team: Biologics

Office of Biotechnology Products (OBP)

- BLA is assigned to primary reviewer, labeling reviewer, Application Technical Lead (ATL)
- Review all non-microbiology product quality information
- Subject matter experts for PLI

Office of Process and Facilities (OPF)

Division of Inspectional Assessment (DIA)

- Review facilities information
- Lead PLI
- Compliance review

Division of Microbial Assessment (DMA)

- Review microbiology information
- Lead PLI

CMC information in the NDA/BLA

- Module 3- Quality
  - 3.2.S- Drug Substance
  - 3.2.P- Drug Product
  - 3.2.A- Appendices
  - 3.2.R- Regional Information
  - 3.3- Literature references

3.2.S.1- General Information
3.2.S.2- Manufacture
3.2.S.3- Characterization
3.2.S.4- Control of Drug Substance
3.2.S.5- Reference Standards or Materials
3.2.S.6- Container Closure System
3.2.S.7- Stability

3.2.P.1- Description and Composition of the Drug Product
3.2.P.2- Pharmaceutical Development
3.2.P.3- Manufacture
3.2.P.4- Control of Excipient
3.2.P.5- Control of Drug Product
3.2.P.6- Reference Standards or Materials
3.2.P.7- Container Closure System
3.2.P.8- Stability

Common Pitfalls

- Certain issues come up repeatedly as information requests, post-marketing commitments (PMCs), or Complete Response (CR) comments during BLA review.
- The following slides highlight some of the most common problem areas.

Risk Assessment

- By the time of BLA submission :
  - The **critical quality attributes (CQAs)*** of the product should be identified and a control strategy in place.
    - Raw material control
    - In-process controls and tests
    - Identification and control of **critical process parameters (CPP)**
    - Release and stability specifications

**ICH Q8 (R2) Pharmaceutical Development*

Case study 1:

- Sponsor defines host cell protein (HCP) as non-critical quality attribute.

- Protein A column flow rate impacts HCP levels, defined as non-critical process parameter because HCP is non-CQA.

- Is this acceptable?

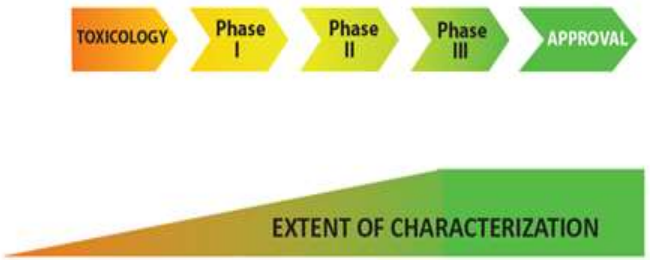
No, HCP can impact safety and immunogenicity and should generally be a CQA. Therefore column flow rate should be a CPP. Sponsor was asked to change classification of both in an information request.

Characterization

- Test material should be representative of the proposed commercial product.
- Common attributes for biologics:
  - Higher order structure, primary AA sequence, heterogeneity (e.g. size, charge, hydrophobicity), glycosylation, post-translational modifications, potency, process related impurities (e.g. host cell protein, DNA, media components).
- Product-related substances ("properties comparable to the desired product", ICH Q6B) versus impurities

Characterization during product development

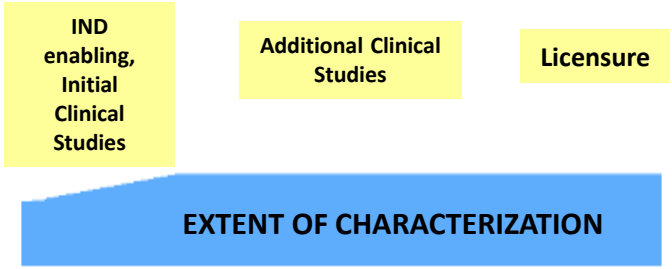
351(a), New Biological Entity



Preliminary product characterization

Extensive product characterization

351(k), Biosimilar



Sufficient data to support proposed product is "similar" to the reference product

Strong evidence to support that proposed product is "highly similar" to the reference product.

LOW DEGREE OF UNCERTAINTY

Draft Guidance for Industry: Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and other Quality-Related Considerations, May 2019

Process Validation (PV)

- "Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product."*
- For therapeutic biologics, PV data should be included in the original BLA.
- **3 components**: Process design, process performance qualification (PPQ), continuing process verification (CPV)
- PPQ: additional in-process testing and monitoring, impurity clearance, hold times.
- Chromatography resin lifetime should be validated at commercial scale.

**FDA Guidance: Process Validation: General Principles and Practices, 2011*

Release Specifications

- Subset of characterization testing
- Chosen to *confirm* the quality, safety, and dosing of future lots (lot-to-lot consistency)*
- Specifications include:
  - List of test, Analytical procedure, Acceptance criteria (numerical limits, ranges, or other criteria)
- Should be established from manufacturing and clinical experience.
- In general, quantitative attributes should have numeric acceptance criteria.
- A final identity test should be performed after all labeling operations are completed (21 CFR 610.14)

Refer to ICH Q6B and 21 CFR 211.160 and 211.165

Stability Data and Specifications

- DS and DP shelf life should be supported by data from a minimum of 3 representative batches under real-time storage conditions.
- Accelerated and stressed conditions should be studied to understand stability indicating attributes and degradation pathways of your product.
- Testing frequency should generally follow ICH Q5C
- Shipping validation studies

Reference Material

- FDA recommends a 2-tier program for in-house reference material.
  - Primary reference material
  - Secondary (working) reference material
- Requalification (stability) protocols should be included in the BLA.
  - Should include: frequency of testing, analytical methods, acceptance criteria, number of replicates, potency measurement, tracking and trending
  - Acceptance criteria are often narrower than release to prevent drift

Case study 2

- Potency of a monoclonal antibody is assigned relative to reference standard in bioassay with 10% variability.
- Release and stability specification for potency is 70-130% of RS.
- WRS Requalification Protocol acceptance criteria of 70-130% of PRS

Is this acceptable?

No, the range is too wide and may allow drift. Requested by the Agency to tighten acceptance criteria in an information request.

Analytical Method Validation

- Non-compendial in-process, release, and stability methods should be fully validated
- Validation parameters include: LOQ, LOD, Linearity, Range, Precision (repeatability, intermediate precision, reproducibility), Accuracy, Specificity

**FDA Guidance: Analytical Procedures and Methods Validation for Drugs and Biologics, July 2015*

- Multiple runs/analysts
- Stability indicating methods should also be validated with stressed/degraded samples
- Compendial methods should be verified under conditions of use (viewed on inspection)

Pre-license Inspection (PLI)

- Scheduled during manufacturing of the product (~4-6 months after submission).
- Confirm commercial production practice adherence to the license
  - Production of biotech API
  - Fill/finish of drug product
  - Contract manufacturers
- Confirm adherence to GMPs
- Assure a robust Quality system
- Quality of contract test labs

Immunogenicity – Anti-drug antibodies (ADA)

- Therapeutic proteins have the potential to induce ADA production.
- ADA can potentially impact safety, efficacy, and pharmacokinetics of the product.
- Binding antibodies- antibodies that bind anywhere on the molecule. Do not necessarily inhibit activity.
- Neutralizing antibodies- binding antibodies that inhibit the biological activity of the molecule.
- Assays to detect ADA should be fully validated for the testing of Phase III clinical samples.
- *Refer to FDA Guidance: Immunogenicity Testing of Therapeutic Protein Products-Developing and Validating Assays for Anti-Drug Antibody Detection, January 2019*

Additional Resources

FDA Guidance for Industry

- *Interpretation of the "Deemed to be a License" Provision of the BPCI Act of 2009*, December 2018
- *Interpretation of the "Deemed to be a License" Provision of the BPCI Act of 2009: Questions and Answers*, December 2018
- *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and other Quality-Related Considerations, May 2019*
- *Process Validation: General Principles and Practices, 2011*
- *Analytical Procedures and Methods Validation for Drugs and Biologics, July 2015*
- *Immunogenicity Testing of Therapeutic Protein Products-Developing and Validating Assays for Anti-Drug Antibody Detection, January 2019*

ICH

- *Q2 Validation of Analytical Procedures*
- *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process*
- *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*
- *Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*
- *Q8 (R2) Pharmaceutical Development*

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