Balajee Shanmugam Ph.D.

Branch Chief (Acting)
Division of New Drug Products I
ONDP/OPQ/CDER/FDA

CDER Regulatory Applications – Investigational New Drug and New Drug Applications

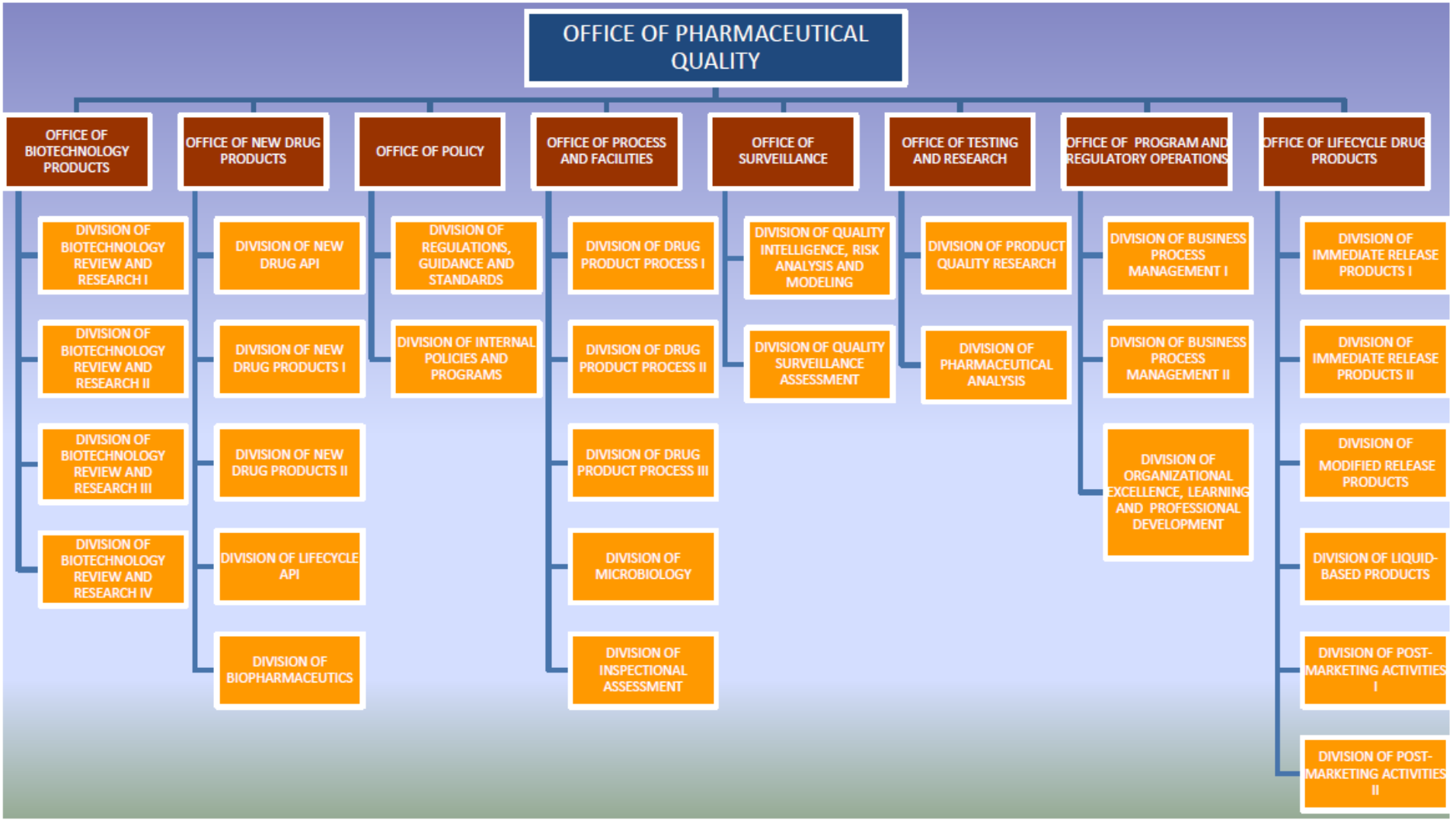
REdI Conference

September 30, 2015

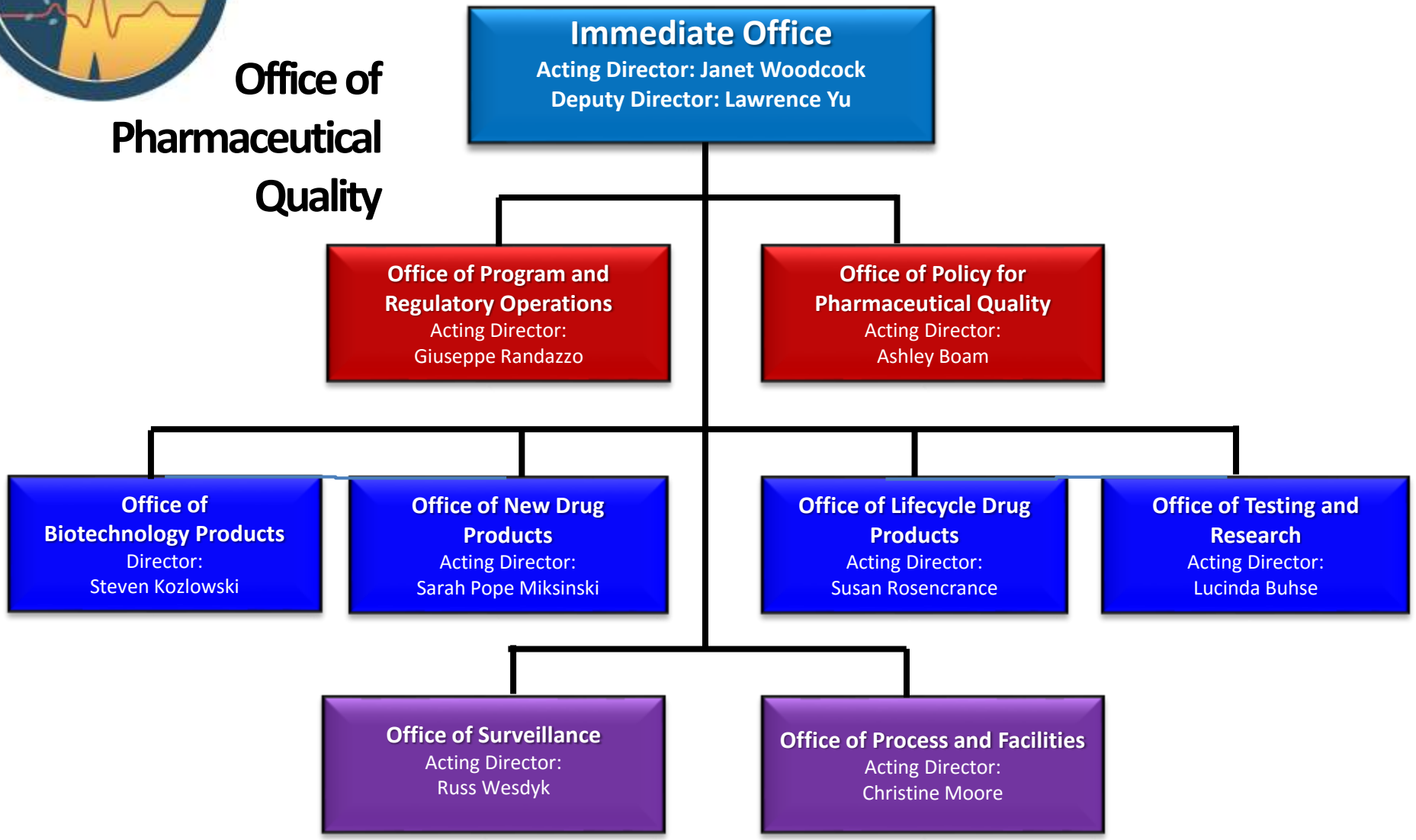
Outline

- Introduction
  - Office of Pharmaceutical Quality (OPQ)
  - Drug Development overview
  - Pharmaceutical Quality and the Desired State
- CDER Regulatory Applications
  - Investigational New Drug (IND) Application
  - New Drug Applications (NDAs)
  - Drug Master Files (DMFs)
- Quality by Design
- Breakthrough Therapies
- Conclusions

CDER Office of Pharmaceutical Quality (OPQ)



Office of Pharmaceutical Quality



Expectations for Quality

Patients and caregivers assume that their drugs:

- **Are safe**
- **Are efficacious**
- **Have the correct identity**
- **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**

What is Pharmaceutical Quality?

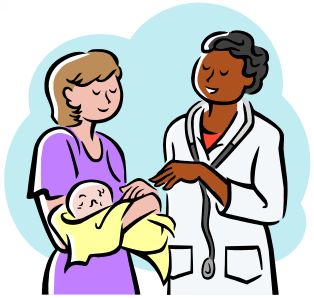
- **The suitability of either a substance or drug product for its intended use. This term includes such attributes as the identity, strength and purity (ICH Q6A)**

Patient & Product

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

Product & Process

Linking Process - Product - Patient



Patient

Quality Target Product Profile

Product

Critical Quality Attributes

Process

Material Attributes & Process Parameters

Why is Quality Important?

- Ties product performance to label claim
- Applies to design, manufacture and clinical use of product
- Relates critical attributes of the drug to patient safety and fitness for use
- Necessary for product availability to patient (i.e., poor quality often results in recalls and shortages)

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)

Agency Meetings/Interactions

- **PreIND**
- **EOP1**
- **EOP2**
- **preNDA**
- **CMC-specific**
- **Others as required**

Everything tracked officially (DARRTS & Panorama)

IND Submission and Review Process

IND Submissions

Initial INDs

- 30 day evaluation period
- Focus on safety
- Safe to proceed or clinical hold
- Some Sponsors elect to withdraw or inactivate rather than be placed on clinical hold

Single patient use (Compassionate use) - ASAP

Treatment INDs and Treatment Protocols

- cGMP evaluation requests submitted
- cGMP recommendation issued within a 30-day clock

Exemptions

IND Submissions – Regulations

21 CFR 312.23(a)(7)(i)

"Sufficient information should be submitted to assure the proper identification, quality, purity, and strength of the investigational drug."

"…the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available."

IND Guidances

- **INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information**
- **Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs**
- **Apply to both research and commercial sponsors of INDs.**

The Initial IND Submission

IND Submission (21 CFR 312)

- Goal: Develop data in humans for submission of an NDA
- Components
  - Cover sheet (21 CFR §312.23(a)(1))
  - Table of contents (21 CFR §312.23(a)(2))
  - Introductory statement and general investigational plan (21 CFR §312.23(a)(3))
    - Brief 2-3 page summary
    - Helps FDA anticipate sponsor needs

The Initial IND Submission (contd.)

- Investigator's brochure(21 CFR §312.23(a)(5))
  - Compilation of the clinical and non-clinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects
  - Facilitates investigator understanding of rationale of key features of the protocol (dose frequency/interval, methods of administration)
- Protocols (21 CFR §312.23(a)(6))
- Chemistry, Manufacturing, and Control (CMC) information (21 CFR §312.23(a)(7))
  - Information on drug substance and drug product

The IND Review Team

- **Primary Clinical reviewer**
- **Primary Quality reviewer**
- **Primary PharmTox reviewer**
- **Sometimes: Clinical Pharm., Microbiology, Biopharmaceutics, Process**
- **Project manager (aligned with the clinical division)**
- **Supervisory/secondary signoffs**

Initial INDs: The Safety Determination

Two possibilities

- **FDA inaction in 30 days implies proposed clinical studies are safe to proceed**
- **FDA issuance of "clinical hold" – no clinical studies can be conducted**

If a study is <u>not</u> determined to be safe to proceed, the IND is placed on "clinical hold."

IND "Safety Issues"

- **Safety issue = a scientific issue which requires data and/or resolution prior to the initiation of the proposed clinical trial(s).**
- **Attempt to resolve all IND safety issues prior to 30-day "safety date".**
- **Unresolved safety issues result in a recommendation for a clinical hold.**

Examples of CMC "Safety Issues"

- Lack of batch analysis (preclinical and/or clinical)
- Insufficient or missing compatibility data
- Inconsistent or deficient CMC information
- Lack of detail regarding manufacturing process
- Lack of sterility assurance
- Lack of proper authorization for cross-referenced information
- Omission of CFR-required CMC items

IND Clinical Holds – Regulations

21 CFR 312.42

- **Order by the FDA to suspend or delay a clinical investigation**
- **Proposed studies may not proceed**

21 CFR 312.42(b)(iv)

"The IND does not contain sufficient information required under § 312.23 to assess the risks to subjects of the proposed studies."

Clinical Holds – Process

During IND safety review (30 days), the CMC reviewer:

- **Confirms required CMC information**
- **Develops a CMC safety recommendation of "safe to proceed" or "not safe to proceed"**
- **Conveys/discusses recommendation to multidisciplinary team**

Clinical Holds – Process

Two possibilities

- **Proposed clinical studies are safe to proceed**
- **FDA issuance of "clinical hold" – no clinical studies can be conducted (issued by clinical division)**

Clinical hold recommendations can also be issued for active INDs during development

Examples of CMC Hold Issues

Potential CMC hold issues during development include:

- **»Stability failures**
- **»New impurities or degradants**
- **»Compatibility issues**
- **»Container integrity issues**
- **»Sterility failures**

Recommended for Hold – What Next?

- FDA correspondence with Sponsor (tcon or written correspondence)
- Occasionally, issues resolved via discussion
- Sponsors may entirely withdraw IND and resubmit at a later time.
- Sponsors may be placed on a “partial hold”.
- Sponsors may be placed on an actual clinical hold.
- Sponsors may elect to inactivate IND until requested information is available.
  - Reactivation required (30 day clock)

IND Amendments (21 CFR 312.31)

- All changes to active INDs are reported to FDA via amendments.
- Routed to CMC Lead; assigned to reviewer as needed
- Many amendments are NAI'd
- Can include request for Agency feedback, or reporting of potential safety issue
- Reviewed under the same 30-day safety evaluation clock
- Typical amendments: minor change in manufacture, batch size change and/or updated batch data, new labeling
- Inspections (cGMP compliance evaluation) can be requested at any time!
- INDs can be placed on hold at any time!

Treatment Protocols

Submitted under an existing IND (21 CFR §312.34)

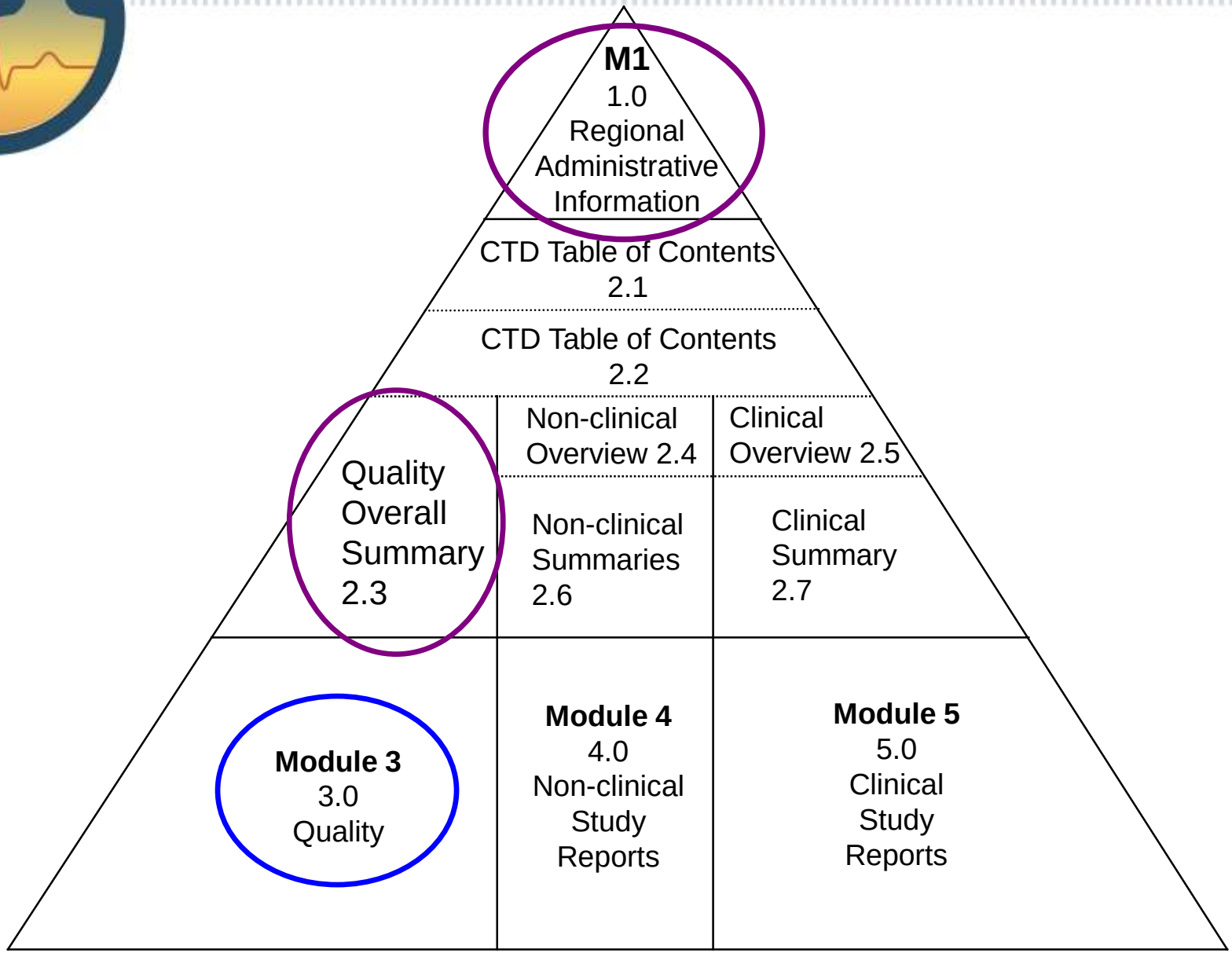
- **FDA shall permit an investigational drug to be used for a treatment use under a treatment protocol or treatment IND if:**
  - **(i) The drug is intended to treat a serious or immediately life-threatening disease;**
  - **(ii) There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population;**
  - **Treatment protocols do <u>not</u> equal intermediate access protocols**

All treatment protocols initiate an Inspection Management (formerly EES) request (30-day clock)

Special Protocol Assessments (SPA)

- 45-day review clock (PDUFA)
- Usually clinical in nature (protocols)
- Occasionally CMC also involved (e.g. stability protocols)

NDA Submission and Review Process


M1
1.0
Regional
Administrative
Information
CTD Table of Contents
2.1
CTD Table of Contents
2.2
Quality
Overall
Summary
2.3
Non-clinical
Overview 2.4
Clinical
Overview 2.5
Non-clinical
Summaries
2.6
Clinical
Summary
2.7
Module 3
3.0
Quality
Module 4
4.0
Non-clinical
Study
Reports
Module 5
5.0
Clinical
Study
Reports

Original NDA Submissions

- CMC information usually included in complete NDA dossier
- Rolling review
  - Discipline sections received subsequently
  - As per previous agreement
  - PDUFA clock starts when NDA submission is complete
- Early submission (21 CFR 314.50)
  - Applies to chemistry

Original NDA Submissions (Cont.)

- **Priority or Standard designation**
  - **Based on clinical impact**
  - **Decided at filing meeting (~45 days post-submission)**
- **60 day filing decision**
- **74-Day letter mandated for early feedback**
- **A very common CMC pre-filing request: confirmation of all manufacturing sites and confirmation of readiness for cGMP inspection**

The NDA Primary Review Team

- Medical Officer
- Integrated Quality Assessment (IQA) team
  - Drug substance, drug product, process, micro, facility reviewer, ORA
  - Biopharmaceutics Reviewer, and other advisors (lab, etc.) as needed
- Statistics Reviewer
- Clinical Pharmacology Reviewer
- Pharmacology/Toxicology Reviewer
- Project Manager (aligned with clinical division)
- Project Manager for Quality
- Supervisory signoffs for all disciplines
- Consults: DMEPA, others as needed

The Complete NDA Submission

Application content and organization (21 CFR 314.50)

1) **Index**
2) **Labeling**
   - **Draft container labels**
   - **"Patient package inserts" (PPIs)**
3) **Application summary**
   - **Statement on pharmacologic class, clinical benefits, and scientific rationale**
   - **CMC information**
   - **Foreign marketing history**

The Complete NDA Submission (cont.)

4) Chemistry
   - Drug substance
     - Physical & chemical characteristics
     - Manufacturer name & address
     - Synthesis and control methods
     - Stability data
   - Drug product
     - Components & composition
     - Batch production records
     - Master production record (21 CFR § 314.420)
     - Manufacturing and packaging procedures
   - Environmental assessment
   - Methods validation package

The Complete NDA Submission (cont.)

5) non-clinical pharmacological and toxicological information
6) human pharmacokinetic (PK) and bioavailability information
7) Microbiology
8) clinical information
9) safety update
10) statistical information
11) case report tabulations
12) case report form submission

The Complete NDA Submission (cont.)

13) patent & exclusivity information

14) establishment description
- Description of manufacturing facilities

15) debarment certification
- Statement confirming that no debarred individual's services were used in connection with the NDA

16) field copy certification
- Statement confirming that a true copy of the chemistry section was submitted to the applicant's home district office

17) user fee cover sheet

18) miscellaneous (i.e. financial disclosure)

The NDA Review Begins…

User fees -- "Prescription Drug User Fee Act" (PDUFA)

- **1992: Fees used to reduce the time required to evaluate certain human drug applications without compromising review quality**
- **1997 (PDUFA II)**
  - **Reauthorized as part of FDAMA through Sept. 30, 2002**
  - **Phased in over five years**
  - **Review times dropped from 1993 to 1997 from 20 months to 12 months**
- **2001/2002 (PDUFA III)**
- **2007 (PDUFA IV, FDAAA)**
- **2012 (PDUFA V, FDASIA)**

Good Review Management Principles and Practices (GRMPs)

- Finalized guidance in April/2005
- Intended to ensure that review and approval process is managed in a consistent and efficient manner
- Based on quality, efficiency, clarity, transparency, and consistency
- Stresses the importance of a complete NDA submission
- Recommends internal FDA review timelines
- Impact on review clock:
    - Internal timelines in place (midcycle, reviews)
    - Internal deadlines often earlier than GRMPs

NDA Refuse to File - Regulations

21 CFR 314.101(a)(1)

"Within 60 days after FDA receives an application, the agency will determine whether the application may be filed. The filing of an application means that FDA has made a threshold determination that the application is sufficiently complete to permit a substantive review."

21 CFR 314.101(d)

FDA Guidance Document: Refuse to File

NDA Refuse to File - Process

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

Example 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 dating period**
- **Significant changes to the commercial formulation following clinical trials**
- **Insufficient parallel between primary stability batches and proposed commercial formulation(s)**

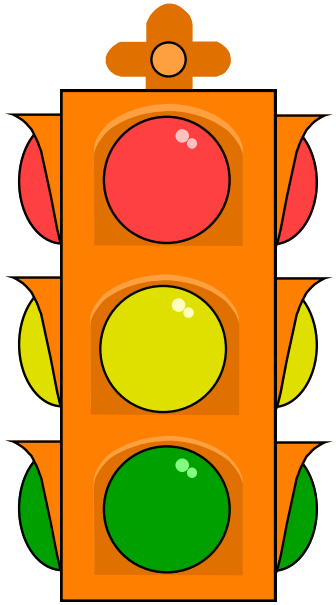
During the NDA Review…

- Pre-approval inspections/cGMP evaluation
- Information requests to Applicant
- Teleconferences as necessary
- Responses sent to Agency for review
  - Timely submissions expected
  - Submissions often governed by previous agreements
  - Submissions received in last 3 months of review clock – possibly considered MAJOR amendments
- Advisory committees (NMEs)
- Labeling review, including container/carton
- Decision on approvability by action due date

NDA Actions

Approval

Complete Response



Information Contained in Action Letter

- Outstanding deficiencies, if any
- Sites receiving withhold recommendations
- Expiration dating period for approvals
- Full labeling, including container/carton labels, for approvals
- Post-marketing studies, as appropriate
- Input from all disciplines – signed off by clinical division or office

Drug Master Files (DMFs)

- Covered under 21CFR 314.420
- Mechanism to preserve confidentiality of proprietary information
- FDA neither independently reviews nor approves or disapproves DMFs
- Types of DMFs:
  - Type 1 [Reserved] Formerly facility descriptions
  - Type 2: Drug substance, drug substance intermediate, and materials used in their preparation, or drug product
  - Type 3: Packaging materials
  - Type 4: Excipient, colorant, flavor, essence, or materials used in their preparation
  - Type 5: FDA-accepted reference information (pre-arranged via letter of intent with FDA).

Drug Master Files (Cont.)

- Can be cross-referenced for either INDs, NDAs or ANDAs
- Letter of Authorization required for cross-reference
- Manufacturing sites included in Inspection Management request for NDAs, ANDAs and supplements
- Separate review conducted for each cross-referenced DMF
- Status of DMF (adequate or inadequate) referenced in NDA, ANDA or IND review document
- DMF deficiencies not specifically conveyed to Applicant or Sponsor!

Quality by Design (QbD)

What is Quality by Design?

Systematic approach to development

- **Applies to both IND and NDA review**
- **Begins with predefined objectives**
- **Emphasizes product and process understanding and process control**
- **Based on sound science and quality risk management**

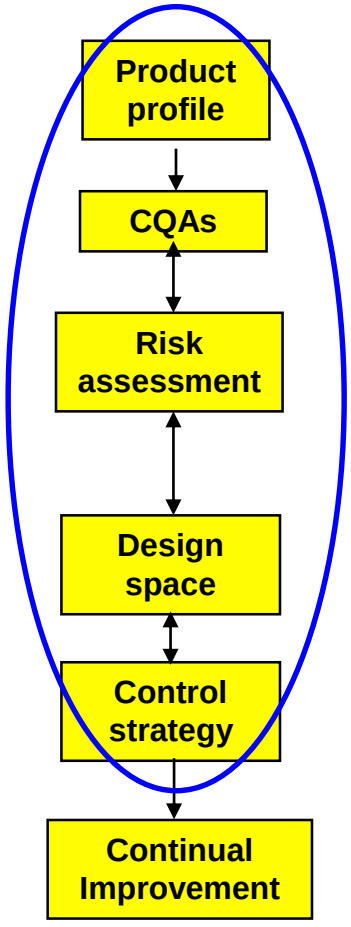
From ICH Q8(R1)

Why QbD?

- Higher level of assurance of product quality
- Cost saving and efficiency for industry
  - Facilitate innovation to address unmet medical needs
  - Increase efficiency of manufacturing process and reduce manufacturing cost and product rejects
  - Minimize/eliminate potential compliance actions, costly penalties and recalls
  - Opportunities for continual improvement
- More efficient regulatory oversight
  - Enhance opportunities for first cycle approval
  - Streamline post approval manufacturing changes and regulatory processes
  - More focused PAI and post approval cGMP inspections

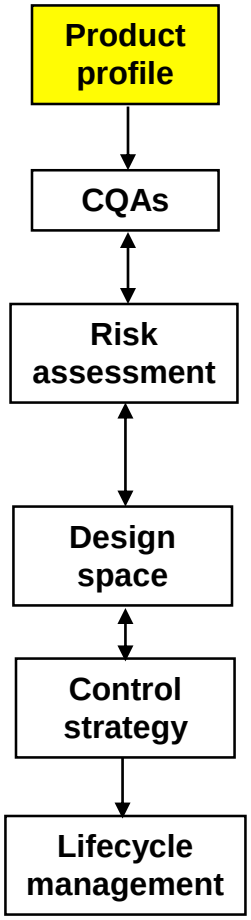

Product Knowledge
Control Strategy/Specifications
Desired Product Performance
Product Quality Attributes
Product Design
Dosage form, stability, formulation, etc.
Process Performance
Cpk, robustness, etc.
Process Controls
Process Understanding
Quality by Design
Process Design
Unit operations, control strategy, etc.
Process Parameters
Continuous Improvement

Example QbD Approach (ICH Q8R1)



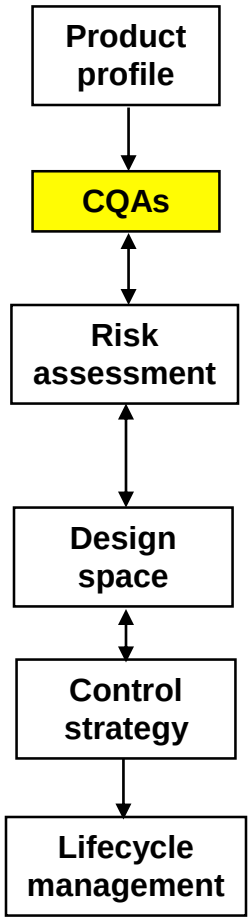
- Quality Target Product Profile (QTPP)
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

Quality Target Product Profile



- Quality Product profile considerations
  - dosage form
  - strengths
  - route of administration
  - release/delivery and pharmacokinetic characteristics
  - specific quality criteria (e.g. sterility, purity)
- Dosage form examples
  - tablets
  - inhalation spray
  - parenteral

Critical Quality Attributes (CQAs)



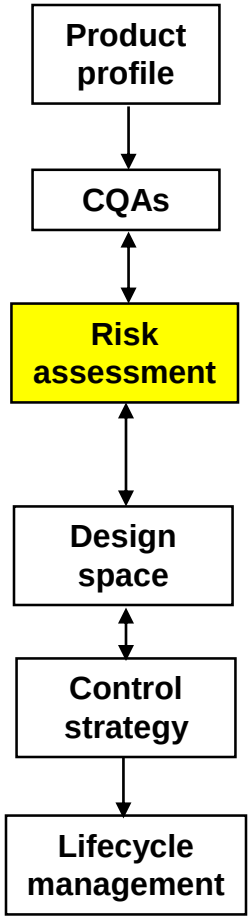
- **Definition (Q8R1)**
  - **A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality**
- **Can describe aspects of drug substance or intermediates that affect drug product quality**
- **Drug product CQAs are used to guide product and process development**

Example of Critical Quality Attributes

-CQA from clinical performance standpoint
- dissolution for extended-release product

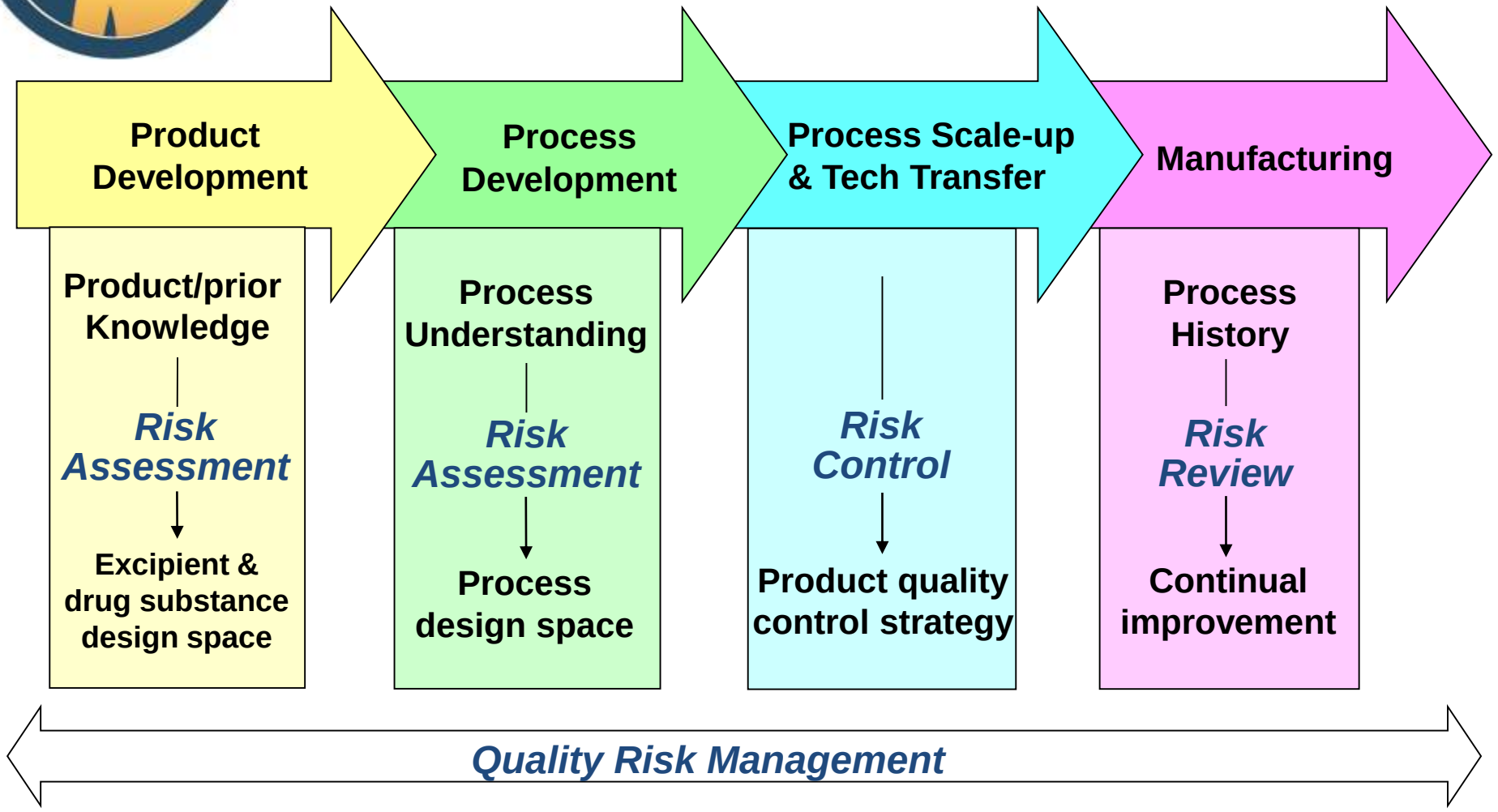
-CQAs from processability standpoint
- tablet hardness
- particle size distribution of blend
- appearance

QbD – Risk Assessment (Q8R1)

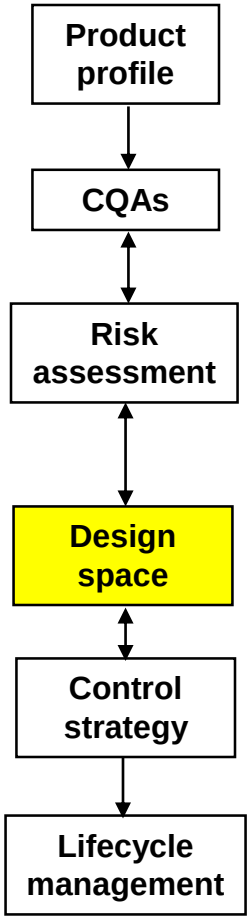


- **Prioritize list of potential CQAs**
- **Aid in identifying and linking material attributes and process parameters which have an effect on CQAs**

Quality Risk Management



QbD – Design Space (Q8R1)



- **Definition**
  - **The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters.**
- **Regulatory flexibility**
  - **Working within design space is not considered a change**
- **Design space is proposed by the applicant and is subject to regulatory assessment and approval**

When to do QbD?

Timing is at Applicant's discretion

- **Phase 1: focus on product understanding**
- **Phase 2: focus on process understanding**
- **Phase 3: apply product and process understanding to manufacture of clinical trial supplies and NDA supportive batches**

Agency interactions: EOP2, pre-NDA, CMC specific meetings (all are encouraged)

How Does QbD Accelerate Development?

More work upfront

- **Systematic**
- **More thorough results**
- **Reduces product failures**
- **Quality control strategies based on product knowledge and process understanding**
- **A more scientific and risk-based approach to regulatory oversight**

You cannot place a price tag on failures that do not occur.

FDASIA - Challenges for Quality Review

- Section 901– Fast Track Drug Products
  - Facilitate development and expedite the review of drugs for the treatment of a serious or life-threatening disease or condition that demonstrates the potential to address unmet medical need
- Section 902 –Breakthrough Therapy Drugs
  - Expedite the development and review of a drug for serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies
    - Provide timely advice and interactive communication with the sponsor regarding the development of the drug to ensure that the development proceeds as planned
    - Provide a collaborative cross disciplinary review utilizing senior managers and experienced review staff, as appropriate
- Section 905 – Risk Benefit Framework
  - Implement a structured risk-benefit assessment framework in the new drug approval process and regulatory decision making

Challenges for Expedited Reviews

- Alignment of CMC development and manufacturing timelines with the clinical development program
  - Consideration of manufacturing scale
  - Coordination with contract manufacturers, as needed
  - Early availability of manufacturing sites for inspection
- Coordination of CMC development program and submissions
  - Recommend early communication between Sponsor and Agency
  - Involve both review and compliance staff to facilitate review and inspection timing
  - Recommend earlier submission of product quality information for review and inspection planning
- Accelerated manufacturing development program likely with less information than typically available
  - May warrant a risk-benefit assessment regarding risk of less CMC information vs. patient benefit

Considerations for Expedited Reviews

- Limited data available and/or submitted
  - Manufacturing batch data
  - Stability data
  - Data available at time of submission
- Review timing constraints
- Frequent communication often needed
- Supply considerations

All rest on…What is the risk to overall quality?

Conclusions

- CMC Evaluation and Recommendation (IND)
  - Safe to proceed
- CMC Clinical Hold recommendations (IND)
  - Based on unresolved CMC safety issues during an IND's safety review
  - Can also be based on safety issues identified during development
- CMC Evaluation of an NDA
  - Complete submission for a substantive review
- CMC Refuse to File recommendations (NDA)
  - Based on an incomplete submission
  - Manufacturing and testing sites not ready for inspection at the time of NDA submission
  - Insufficient (or missing) stability data

Conclusions

- **Quality by Design – a more scientific and risk-based approach to regulatory oversight**
- **Some challenges with expedited/priority therapies**
  - **Alignment of CMC and clinical development**
  - **Sometimes warrants a risk/benefit assessment regarding risk of less CMC information vs. patient benefit**
- **Proactive communications encouraged during development and review**
- **FDASIA will help bring promising therapies sooner**

Acknowledgements

- Sarah Pope, Ph.D., Director (Acting), Office of New Drug Products
- Christine Moore, Ph.D., Director (Acting), Office of Process and Facilities
- Ramesh Sood, Ph.D., Senior Scientific Advisor (Acting), Office of New Drug Products
- Robert Iser, Director, Division of Process Assessment III & Senior Scientific Advisor, Office of Process and Facilities

Thank You!

Questions?

Please complete the session survey:

surveymonkey.com/r/DRG-D2S4