

# **Risk and Team-based Integrated Quality Assessment in the Office of Pharmaceutical Quality**

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**M. Scott Furness, Ph.D.**

Deputy Director, Office of New Drug Products  
Office of Pharmaceutical Quality/CDER/FDA

# Outline

- Introduction - Office of Pharmaceutical Quality (OPQ)
  - The Integrated Quality Assessment (IQA) process
- Introduction - Office of New Drug Products (ONDP)
- Clinical relevance
- Risk based CMC review

# Office of Pharmaceutical Quality (OPQ)

- Organization stood up on January 11, 2015.
- Combined components of the former CDER Office of Pharmaceutical Science (OPS) and CDER Office of Compliance
- Expected to provide better alignment among all drug quality functions at CDER, including review, inspection, and research.

# CDER OPQ

- Focus areas for new office:
  - Integrated approaches for review and inspection
  - Risk based approaches to review and inspection
  - Modern regulatory science approaches (e.g., clinically relevant specifications, etc.)
  - Implement a lifecycle approach to quality
  - Improve data management and surveillance

# CDER OPQ

## **Mission**

*The Office of Pharmaceutical Quality assures that quality medicines are available to the American public*

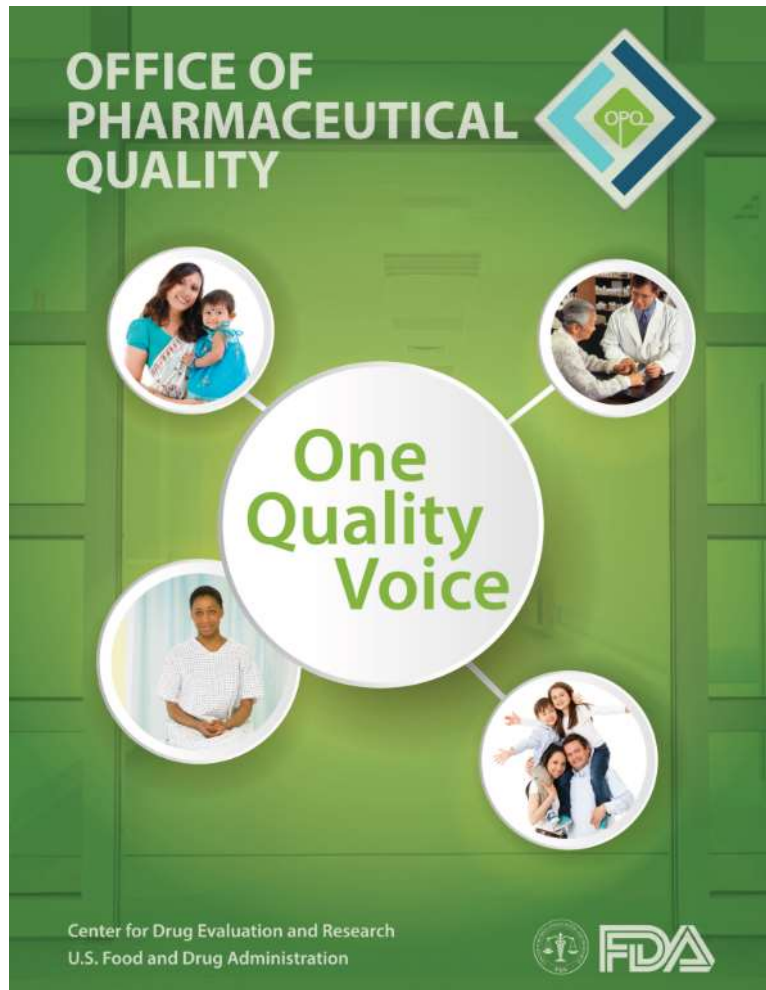
## **Vision**

*The Office of Pharmaceutical Quality will be a global benchmark for regulation of pharmaceutical quality*

## **One Quality Voice**

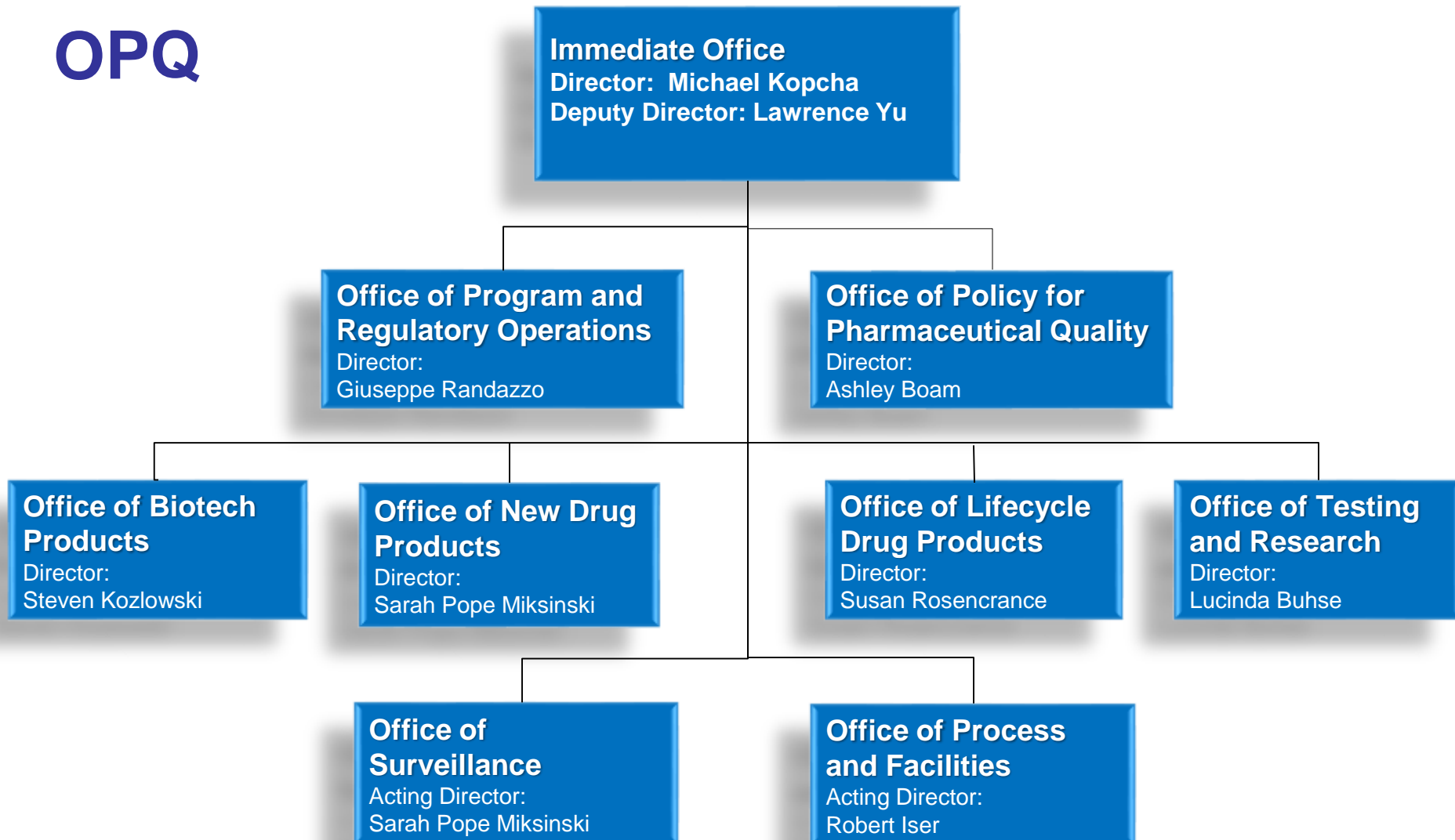


# “One Quality Voice”



- Put patients first by balancing risk and availability
- Have one quality voice by integrating review and inspection across product lifecycle
- Safeguard clinical performance by establishing scientifically-sound quality standards
- Maximize focus and efficiency by applying risk-based approaches
- Strengthen the effectiveness of lifecycle quality evaluations by using team-based processes
- Enhance quality regulation by developing and utilizing staff expertise
- Encourage innovation by advancing new technology and manufacturing science
- Provide effective leadership by emphasizing cross-disciplinary interaction, shared accountability, and joint problem solving
- Build collaborative relationships by communicating openly, honestly, and directly

## OPQ



# OPQ

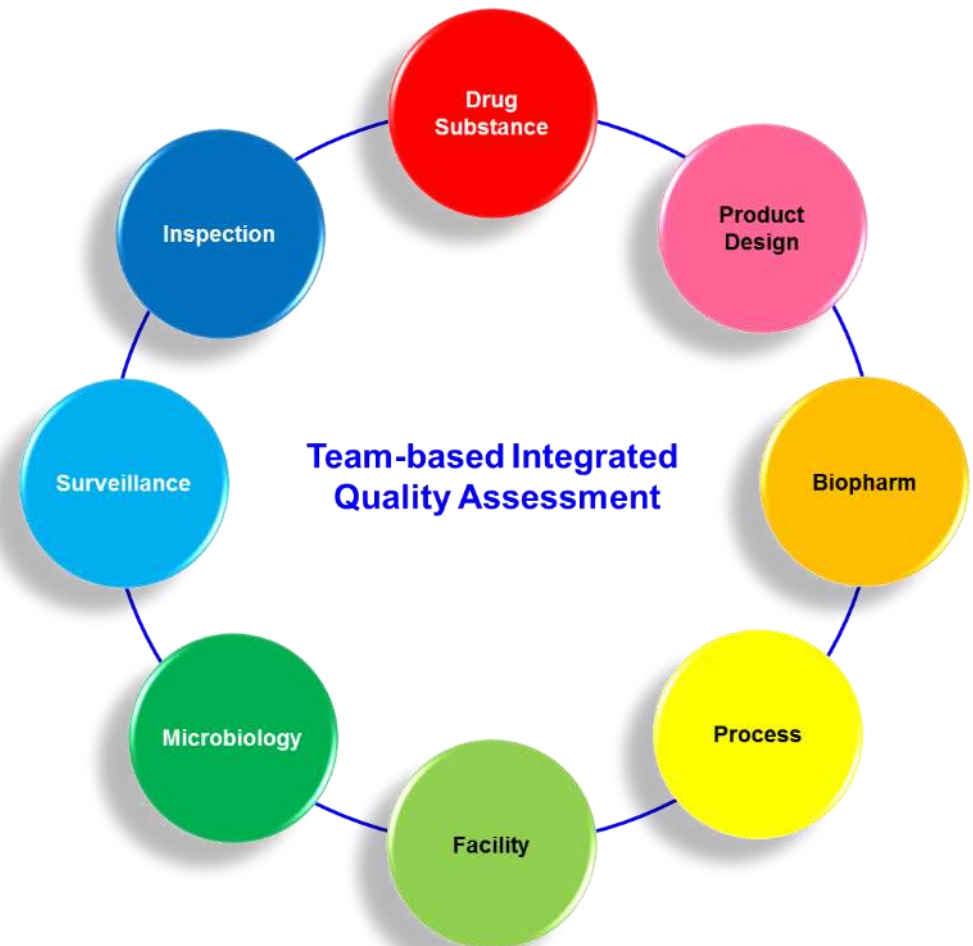
- To keep pace with increasing product complexity, OPQ is organized based on discipline and subject matter expertise
- Matrices the review function across OPQ for enhanced interactions, communication, and consistency among sub-offices
- Aligns functional areas for the purpose of streamlining FDA processes that monitor drug quality





# Team-based Integrated Quality Assessment (IQA)

A team of subject matter experts performing a quality assessment (review) of an application (NDA, BLA, ANDA) based on risk management principles



# How is IQA different from previous process?

- OPQ process uses:
  - subject matter expert teams
  - concurrent assessment
  - single review template
  - scheduled team meetings
- Pre-OPQ process uses:
  - “one application, one reviewer”
  - independent assessment
  - separate templates
  - inconsistent communication between disciplines



## Previous Review Process

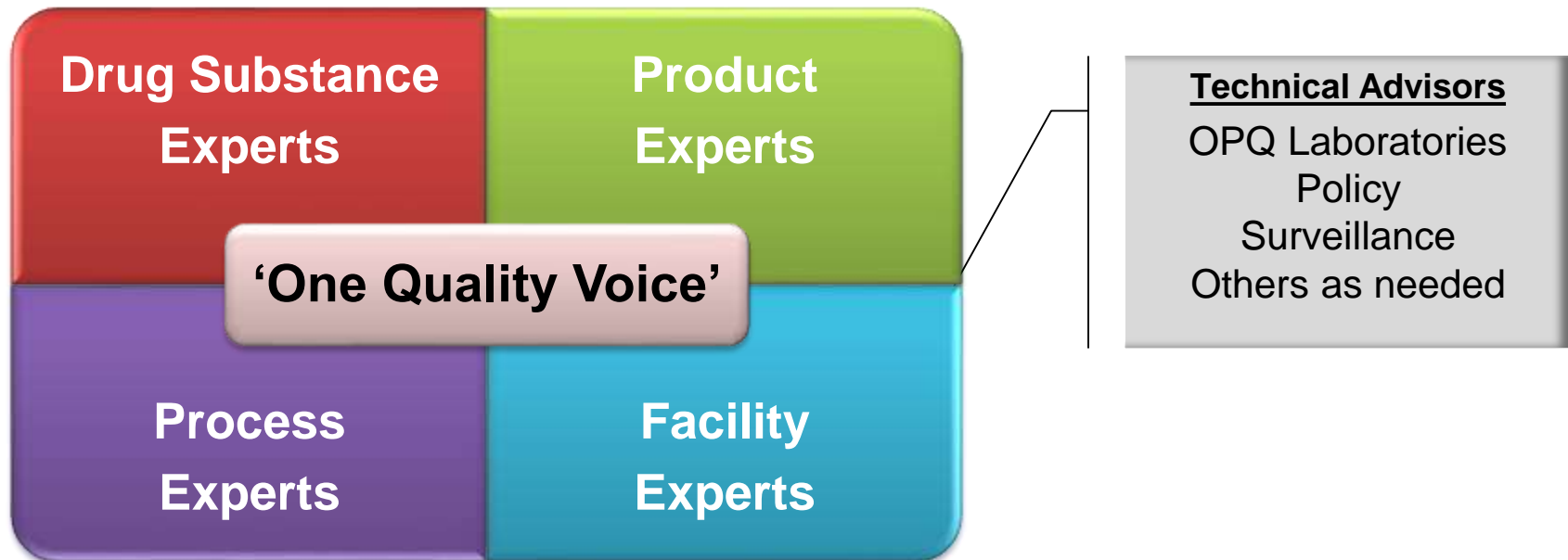
- No formal risk assessment process to define scope and extent
- Discipline reviewers worked in isolation
- Independent reviews (or assessments)
- Separate review templates
- Rare communications between review functions and facility inspections

## Team-based Integrated Quality Assessment

- Formal risk assessment process to enhance efficiency and effectiveness of review and inspection
- Team of discipline reviewers with constant communication
- A single collaborative review (or assessment)
- Consolidated review template
- Integration of review with inspection for more informed decisions on facility acceptability and application approvability

# The IQA Review Team

## Discipline Reviewers



**Application Technical Lead (ATL)** – oversees the scientific content of the assessment

**Business Process Manager (BPM)** – manages the process, adhering to the established timelines

# The Integrated Quality Assessment (IQA)

**OPQ**

**Integrated  
Quality  
Assessment**

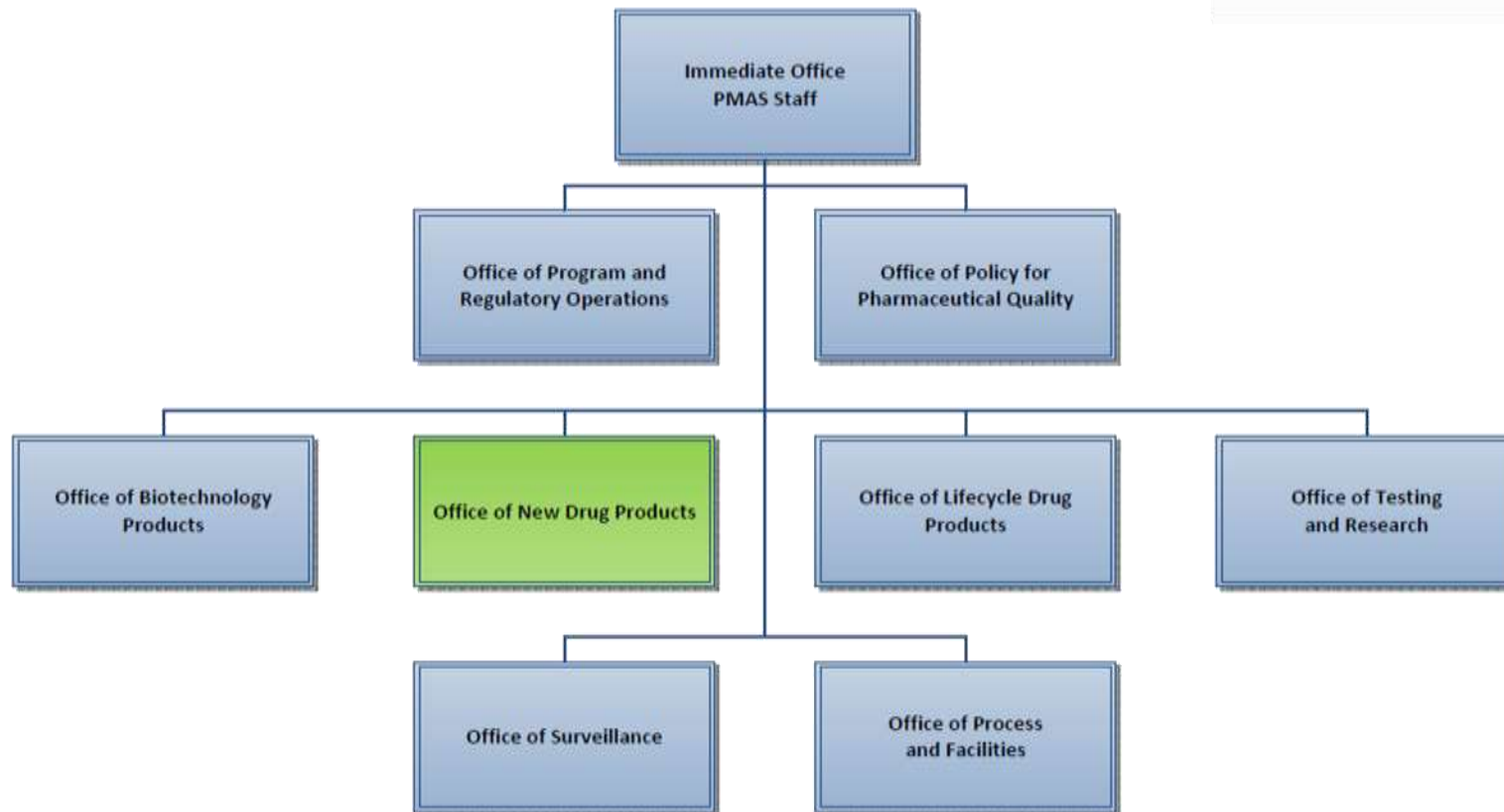
A single integrated  
recommendation on  
application approvability



**OGD**

**OND**

# THE OFFICE OF PHARMACEUTICAL QUALITY



# Introducing the Office of New Drug Products (ONDP)

## Office of New Drug Products (ONDP)

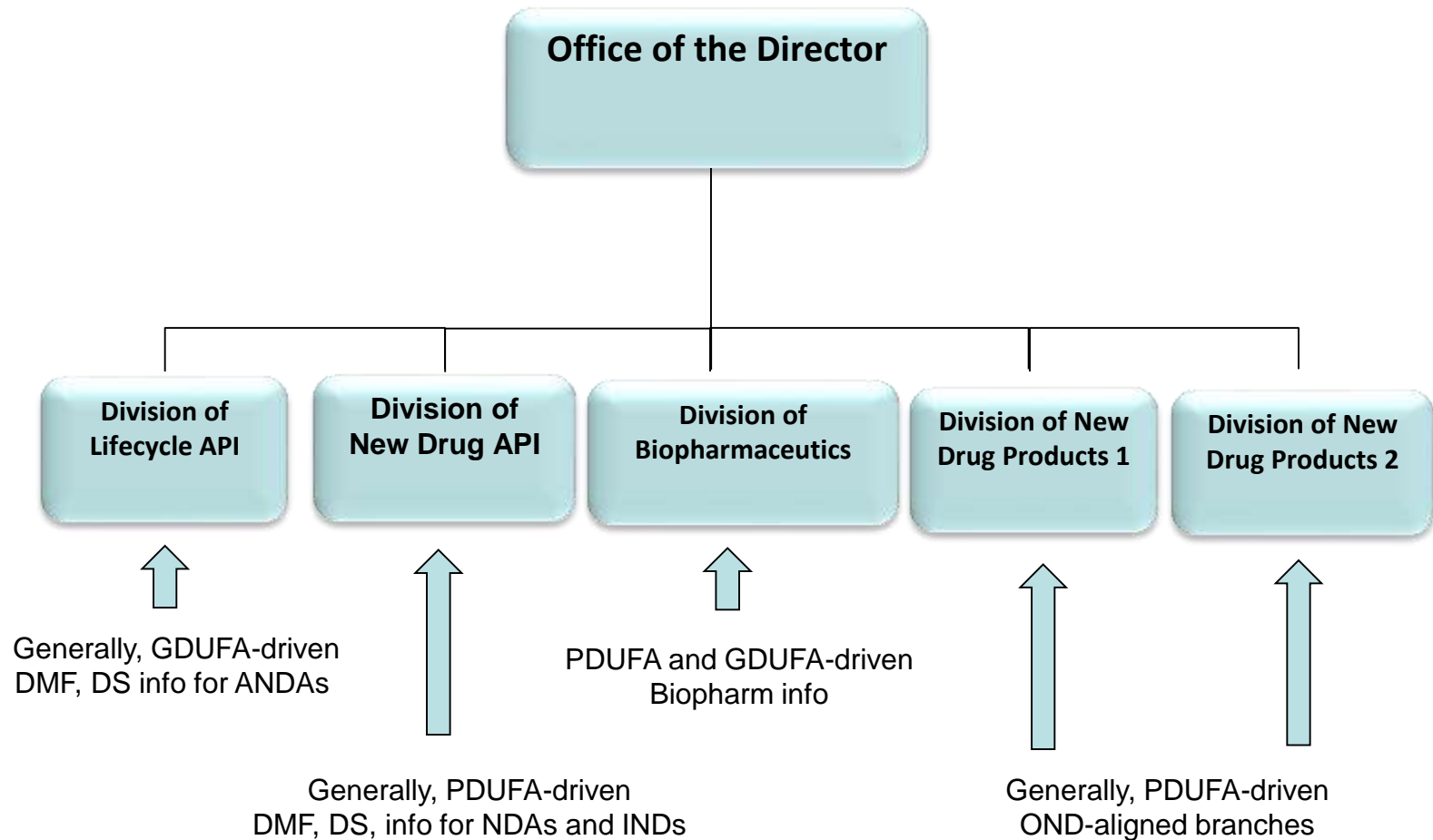
The Office of New Drug Products (ONDP) conducts **risk and team-based, cross-office collaborative** quality assessment of Investigational New Drug (IND) submissions, original and some supplemental New Drug Application (NDA) submissions, and active pharmaceutical ingredient (API) information supporting all new and supplemental NDAs and Abbreviated New Drug Applications (ANDAs). ONDP also assesses the biopharmaceutics portion of INDs, NDAs, ANDAs, and their associated supplements.



## ONDP Specific Functions

- Convey **risk-informed recommendations** on product quality to CDER offices and industry
- Communicate **product risk** in the pre-marketing stage of assessment
- **Collaborate** with other OPQ offices to conduct **integrated quality assessments**
- Serve as quality liaison to the Office of New Drugs
- Participate in inspections as needed

# Office of New Drug Products (ONDP)



# ONDP Immediate Office

- Sarah Pope Miksinski (Director)
- Scott Furness (Deputy Director)
- Ramesh Sood (Acting Senior Scientific Director)
- Margaret Caulk (Associate Director for Science and Communication)

# ONDP Division Directors

- Dave Skanchy (Division of Lifecycle API)
- Ali Al Hakim\* (Division of New Drug API)
- Paul Seo\* (Division of Biopharmaceutics)
- Tom Oliver\* (Division of New Drug Products I)
- Eric Duffy (Division of New Drug Products II)

\*Acting position

# Clinical Relevance

- Product quality = the foundation upon which clinical safety and efficacy assessment depend
- Integration of quality and clinical assessment
- Without clinical linkage, acceptance criteria could be too wide, too tight or irrelevant
- A product is “fit for use” by meeting established quality attributes (purity, potency/strength, identity, bioavailability/delivery, labeling/packaging, etc.)
- Strive to establish appropriate correlations between quality attributes and clinical performance

# Clinical Relevance

- Quality attributes
  - Critical –with proper clinical linkage
  - Others – to assure robustness and performance of manufacturing process and patient expectations
  - Possible surrogate markers of intended clinical performance
- Clinical considerations
  - Urgency (BT, otherwise expedited)
  - NTI
  - Pediatric
- IVIV correlation/relationship
  - Dissolution testing

# Clinical Relevance in Quality Review

Incorporates a robust and broad dialog

- Clinical framework (e.g. urgency)
- Regulatory framework (review deliverables)
- Supporting technical information
- Appropriately considers prior knowledge
- Strong collaboration for common understanding
- Lifecycle management considerations
- Other aspects of “the patient at the table”
- Transparent and effective risk-informed discussions
  - One Quality Voice

# Clinically Relevant Specifications (CRS)

- Similarly broad and robust discussion
- Begins with supporting data platform
- Discussion considers needs of stakeholders
  - What do we get?
  - Will not or can not?
  - Nice to know or need to know?
- Takes existing knowledgebase into account
  - IVIVC/R
  - Dissolution method/criteria
  - Physiology/physicochemical properties
  - Safety data (e.g. qualification data for impurities)



# Clinically Relevant Specifications (CRS)

- Discussion transparently addresses uncertainty
  - What do we know?
  - What are we uncertain of?
  - What is the impact of the uncertainty?
- Considers whether/how uncertainty can be mitigated
- Considers whether uncertainty needs to be mitigated
- Considers the possibility of mitigating outside of specification adjustments

# **An example - Impurities**

## Clinical Relevance - Impurities

- Existing CMC guidances provide significant recommendations based on clinical relevance associated with impurities:
  - *ICH Q3A: Impurities in New Drug Substances*
  - *ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*

# Clinical Relevance - Impurities

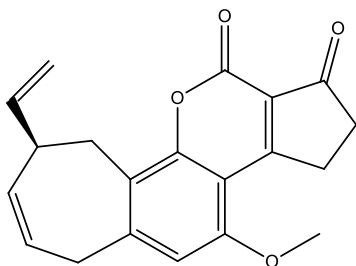
- Current ICH Q3A Guidance (Impurities in New Drug Substances):
  - “Higher or lower thresholds for qualification of impurities can be appropriate for some individual drugs based on scientific rationale and level of concern, including drug class effects and clinical experience.... a higher qualification threshold can be appropriate for individual drugs when the level of concern for safety is less than usual based on similar considerations (e.g., patient population, drug class effects, clinical considerations).”
  - The standard identification and qualification thresholds described in this guidance are inversely proportional to the maximum daily dose of the drug (i.e., the higher the maximum daily dose, the lower the threshold values).

# Clinical Relevance - Impurities

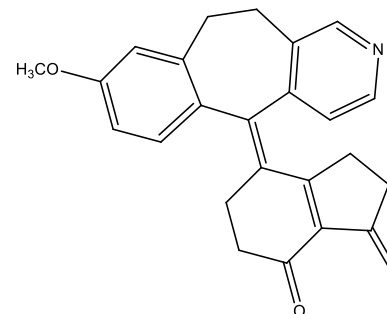
- Current ICH M7 Guidance (Assessment and Control of Mutagenic Impurities):
  - “There may be some cases where a drug substance intended for other indications is itself genotoxic at therapeutic concentrations and may be associated with increased cancer risk...exposure to a mutagenic impurity would not significantly add to the cancer risk of the drug substance.”
  - Higher acceptable intakes may be justified:
    - when human exposure to the impurity is much greater from other sources e.g., food, or endogenous metabolism (e.g., formaldehyde)
    - in cases of severe disease, reduced life expectancy, late onset but chronic disease, or with limited therapeutic alternatives
    - based on a risk/benefit analysis when control efforts cannot reduce levels below the acceptable limit

# Mock Example – ICH M7 Case Study

- Treatment duration: < 1 day
- Treatment duration: Lifetime



- Parent drug is a short-acting intravenous anaesthetic agent used for the induction of general anesthesia for short procedures such as reduction of dislocated joints and tracheal intubation
- **Acceptable daily intake 120  $\mu\text{g}/\text{day}$**



- Parent drug is indicated for the symptomatic relief of allergy such as hay fever (allergic rhinitis), urticaria (hives), and other skin allergies.
- **Acceptable daily intake 1.5  $\mu\text{g}/\text{day}$**

# Why Risk Based Review?

- One of the foundational pillars of OPQ is using risk based approaches in our reviews, which will aid in:
  - Efficiency and effectiveness of review
  - Addressing increasing workload (NDAs, ANDAs, INDs, Meetings)
  - Priority Reviews
  - Review of applications with Breakthrough designation (BT)
    - Urgent need for availability of such drugs
    - Further shortening of review times
    - Increased resources to meet Breakthrough designated drugs development and approval
  - Communication between offices and disciplines
  - Knowledge management
  - To ensure availability of fit-for-use, quality drugs for patients.

# Traditional CMC Risk Assessment

- **The Agency has always considered CMC risk in review of every application!**

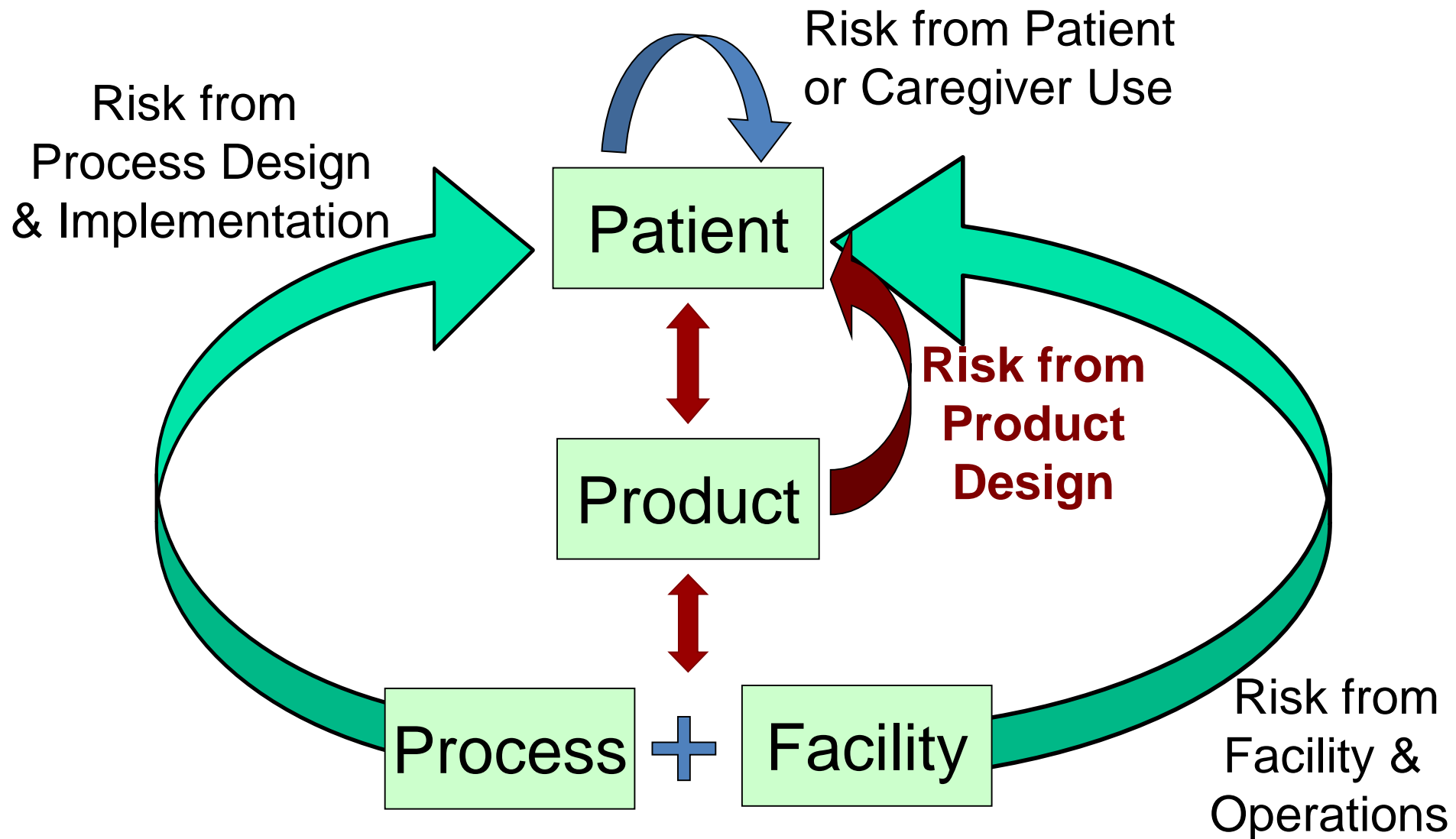
## **HOWEVER....**

- Reviewers evaluated and documented risk on an informal basis
  - No clear easily accessible location in the review
  - Not systematic, could be incomplete
- We reviewed to current manufacturing process and controls
  - Not forward looking
  - Some QbD containing applications an exception
- No forward-looking Life-Cycle Knowledge Management system
  - No standard system
  - Not updated as process changes
  - Often need to read entire review history



# Objective of Risk Based CMC Review

- Understanding the inherent risk of different types of products to the patient could allow for:
  - More efficient review processes
    - Focus on the most critical aspects
  - More efficient and targeted inspections
    - Focus on the most critical processes and facilities
  - Easier post approval changes
    - Reduction of supplements
    - Enable effective continual improvement



# Product Risk Ranking Approach

- Collected Lists of Critical Quality Attributes (CQAs)
- A Failure Mode and Effects Analysis (FMEA) approach was used for each CQA, based on potential harm to patient
- To attempt to be process independent, a worst case scenario for typical manufacturing was considered
  - **Standard sampling and appropriate analytical methods were assumed**
  - **Did not consider aspects such as deliberate adulteration or data manipulation**
- Product Risk established using a combination of Likelihood of Occurrence, Severity (to patient), and Detectability

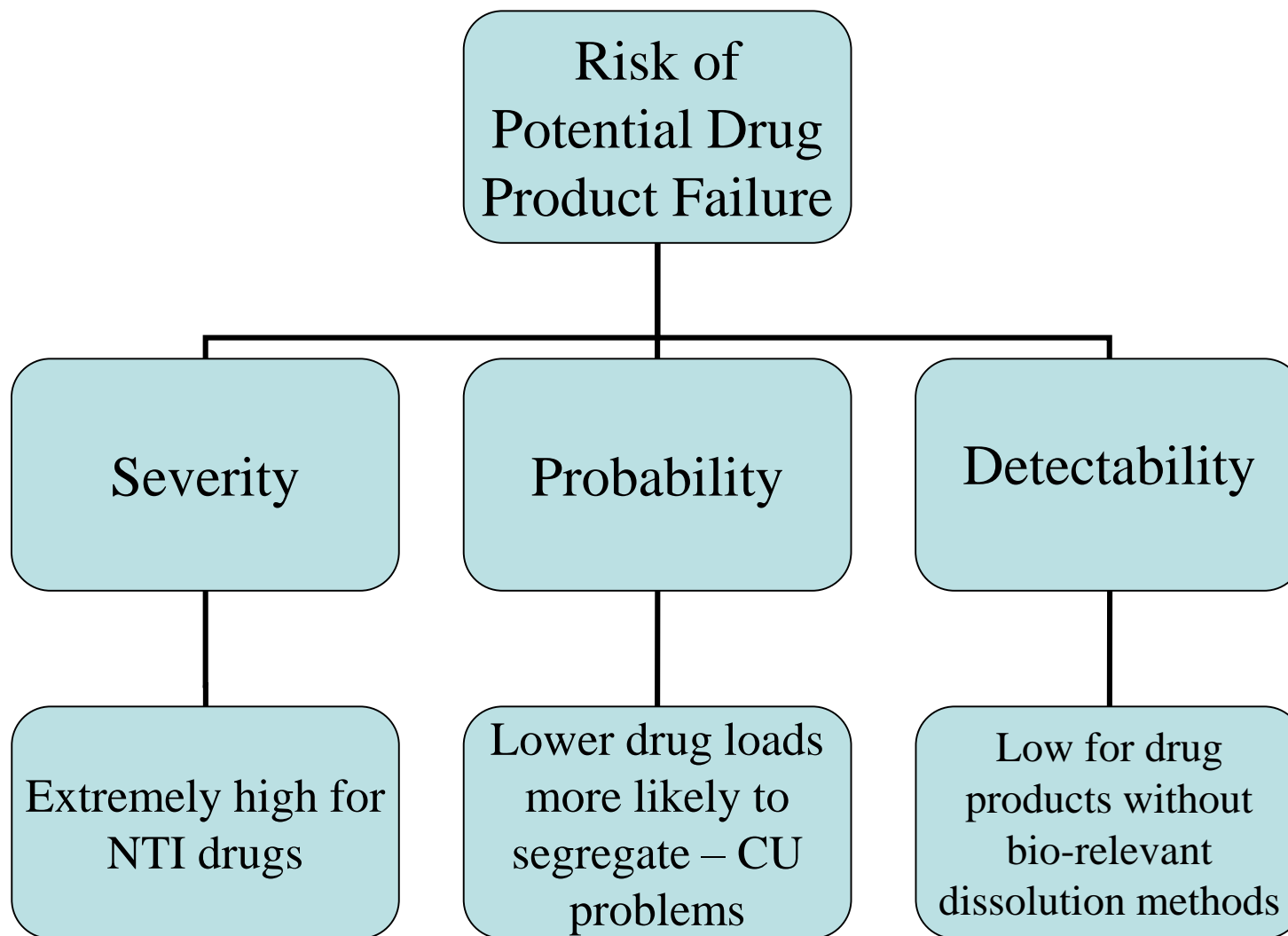
# Elements of Product Risk Ranking

- Severity (S) – Potential effect observed **by the patient**
  - Related to drug and dosage form; independent of process or facilities
  - Assumes standard patient population
  - Considers both immediate and potential long term consequences
- Occurrence (O) – Based on probability of fault **upon unspecified change**
  - Based on prior knowledge of manufacturing, assuming “worst case” under typical operating conditions, current agency’s NDA and ANDA data (e.g. surveillance)
  - Considers both observed and potential occurrence (based on prior knowledge)
- Detectability (D) – Ability **of manufacturer** to detect faults through **routine/standard procedures**
  - Based on knowledge of analytical method capability, representativeness and typical sampling approaches

# CQAs Evaluated - Example

- Solid Oral Dosage Forms
  - Assay, Chemical Stability
  - Physical Stability
  - Content Uniformity
  - Dissolution
  - Microbial Limits
  - Disintegration for orally disintegrating tablets
  - Friability, Dissolution and Content Uniformity for functionally scored tablets
  - Bead size for sprinkles
  - Delamination for multilayer products
  - Alcohol Dose dumping for modified release
  - Leakage from soft gelatin capsules
  - Antioxidant & Preservative for soft gelatin capsules
  - Palatability for chewable and orally disintegrating
  - Tablet hardness for chewable tablets

# CQA Initial Risk Evaluation



# Risk Assessment: Areas for Improvement

Drug Product CQAs	Initial Risk Ranking FMECA Score	Comments	Updated Risk Ranking after Review Cycle #	Comments
CQA1				
CQA2				
CQA3				
CQA4				
CQA5				
Other CQAs				

**“Objective” Initial FMECA Risk Scoring Algorithm in Place**

**Risk Mitigation Still Highly Subjective Elements**

**Common Area of Confusion/Misunderstanding**

**Highly Dependent on Review Opinion/Expertise**

**Difficult to Extract and Rate from an Inventory of 1000s of NDA/ANDA Application Reviews**

# Future Direction - Quality Dashboard Based upon Drug Product Risk Mitigation

CQA	Universal Sources of Variability	Risk Mitigation Strategies	Explanatory Comments
Content Uniformity	Drug Product Design	Risk Mitigation Menu Similar API and Excipient PS Similar API and Excipient Bulk Densities Adsorption of API onto Carrier Excipient Other	Drop-Down menu of "Common" Risk Mitigation <b>DESCRIPTORS</b> Relevant to each CQA  <b>Descriptor: Structured Knowledge of Formulation/Process Design and/or Control Strategy</b>
	Manufacturing Process/Equipment	Risk Mitigation Menu Process design Scale-up plan Other	
	Measurement System	Risk Mitigation Menu PAT Monitoring for Tablet Uniformity Extensive Stratified Sampling (100 Units) Other	
Dissolution	Drug Product Design	Risk Mitigation Menu	
	Manufacturing Process/Equipment	Risk Mitigation Menu	
	Measurement System	Risk Mitigation Menu	
Chemical Stability	Drug Product Design	Risk Mitigation Menu	
	Manufacturing Process/Equipment	Risk Mitigation Menu	
	Measurement System	Risk Mitigation Menu	



# Quality Dashboard: Structured Descriptors of Risk Mitigation Strategies Capture State of Quality Risk Approved NDAs/ANDAs

Same Drug Product

CQA	Initial Risk	Universal Source of Variability	Risk Mitigation Strategy	Residual Risk Remaining
Content Uniformity	High	Product Design	No strategies demonstrated	Medium (High)
		Process	No strategies demonstrated	
		Measurement	Traditional CU USP <905>	
CQA	Initial Risk	Universal Source of Variability	Risk Mitigation Strategy	Residual Risk Remaining
Content Uniformity	High	Product Design	Similar API and Excipient PS for Blending Unit Operation	Medium
		Process	No Strategies Demonstrated	
		Measurement	Traditional CU USP <905>	
CQA	Initial Risk	Universal Source of Variability	Risk Mitigation Strategy	Residual Risk Remaining
Content Uniformity	High	Product Design	Similar API and Excipient PS for Blending Unit Operation	Low
		Process	CPPs well understood and controlled	
		Measurement	Stratified Sampling Maintained During Commercialization	

ANDA x

ANDA y

NDA

Increasing Level of Monitoring Scrutiny

Supplements And Manufacturing Surveillance

# Potential Utility of Drug Product Quality Dashboard

- Quickly Rank Relative Product Risks ANDA/NDAs
- Guide Supplement Risk Evaluation
  - (Living Document based upon Supplements Approved in Product Lifecycle)
- Input for Surveillance Risk Model =  $f$  (Facility Risk,  $g$  (Quality Risk))

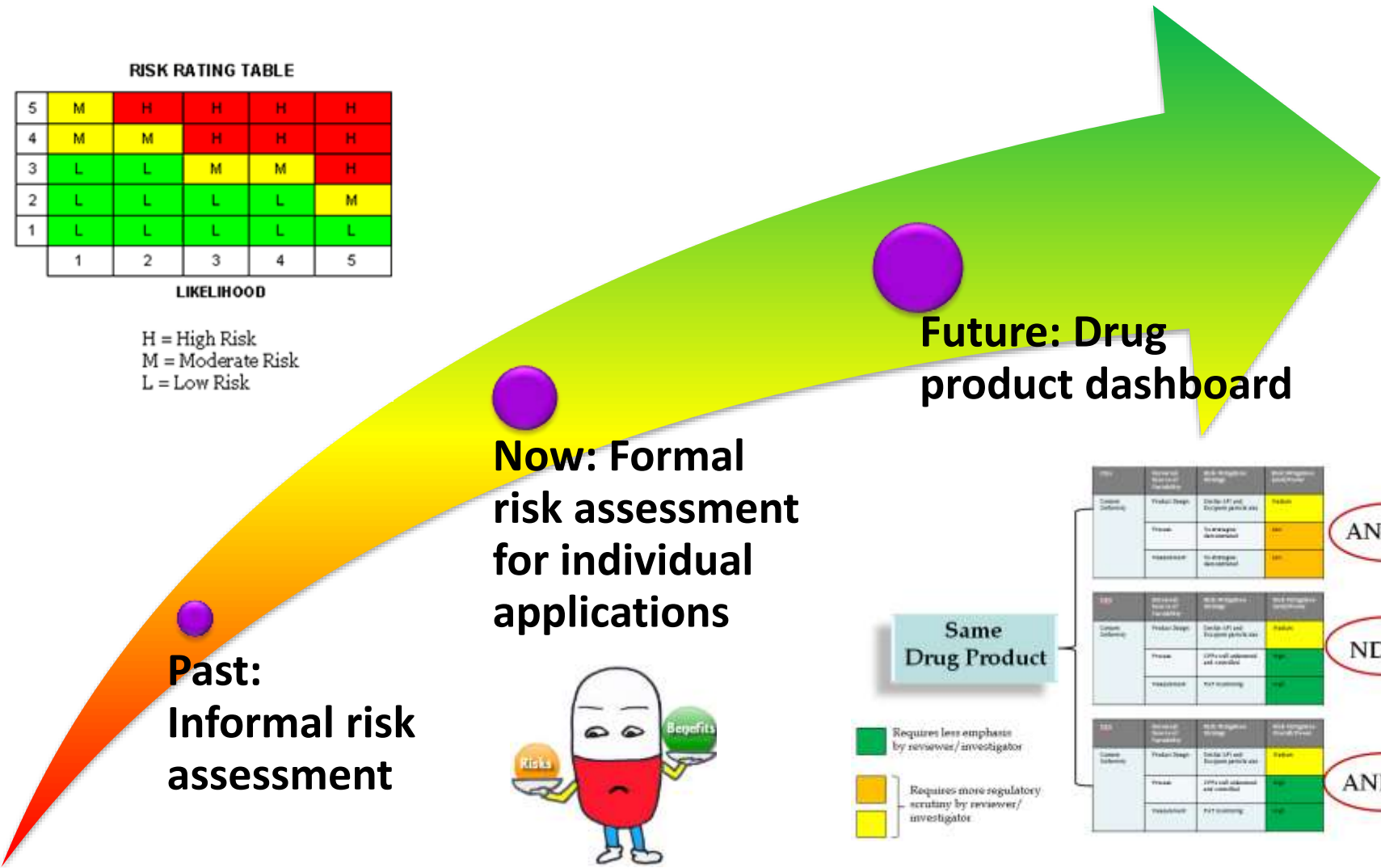
OPQ Mission  
Pharmaceutical Quality Informatics

# Summary: CMC Risk Management

**RISK RATING TABLE**

IMPACT	5	M	H	H	H	H
	4	M	M	H	H	H
	3	L	L	M	M	H
	2	L	L	L	L	M
	1	L	L	L	L	L
		1	2	3	4	5
		LIKELIHOOD				

H = High Risk  
M = Moderate Risk  
L = Low Risk



**Future: Drug product dashboard**

**Now: Formal risk assessment for individual applications**

**Past: Informal risk assessment**

Same Drug Product				
IMPACT	Individual New Active Ingredient	MRM: Significant Change	MRM: Significant Change	
Critical (red)	Product Design	Control LPT and Excipient particle size	High	ANDA x
	Process	Manufacturing data control	High	
	Manufacture	Manufacturing data control	High	
Major (yellow)	Product Design	Control LPT and Excipient particle size	Medium	NDA
	Process	CMR cell assessment and control	High	
	Manufacture	CMR cell assessment and control	High	
Minor (green)	Product Design	Control LPT and Excipient particle size	Low	ANDA y
	Process	CMR cell assessment and control	Low	
	Manufacture	CMR cell assessment and control	Low	

Requires less emphasis by reviewer/investigator  
Requires more regulatory scrutiny by reviewer/investigator

## Conclusion – Risk Based CMC Review

- Formal risk assessment is a key focus area for the new Office of Pharmaceutical Quality (OPQ)
- Formal risk management approaches are being used in CMC review to ensure that all high risk areas receive appropriate scrutiny to ensure the availability of high quality drugs.
- Potential Future Direction - Formalized Structured Risk Mitigation Dashboard
  - Tool for Lifecycle Management (Supplement Risk Evaluation)
  - Tool for Picture of “Quality” of Drug Product Inventory

# Questions?

Please complete the session survey:

[surveymonkey.com/r/DRG-D2S5](https://surveymonkey.com/r/DRG-D2S5)

# Thank You



[CDER-OPQ-Inquiries@fda.hhs.gov](mailto:CDER-OPQ-Inquiries@fda.hhs.gov)