New Drug Applications: The Evolution of Quality Review

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Outline

- Quality expectations and risk considerations
- Integrated Quality Assessment for NDAs
  - History/Previous observations
  - Team structure
  - Operations
- General considerations
  - The link to the patient (how?)
  - Information Requests (IRs)
  - Risk communication
- Conclusions

Expectations for Quality

Patients and caregivers assume that their drugs:

- Are safe, efficacious, and 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

Linking Process - Product - Patient

Patient → **Product** → **Process**

Quality Target Product Profile → **Critical Quality Attributes** → **Material Attributes & Process Parameters**

Team Review for NDAs - History

- 2005
  - CMC Pilot (QbD)/ONDQA
- 2008 through 2012
  - Multiple expedited reviews, advanced technologies
- 2012 to current
  - Breakthrough Therapies
- 2013 to current
  - Integrated Team Review/Team-Based Integrated Quality Assessment (IQA)

Reviews as a Team-Based Process

- Previous team-based reviews
  - Typical NDA review team
    - Primary reviewers – Both CMC and Biopharmaceutics
    - QbD Liaison
    - ONDQA Project Manager
    - Supervisors (Branch Chief, Division Director)
    - Additional technical experts – Statistician, Microbiologist (as needed)
- Expanded review and inspection team
  - Office of Compliance (OC) – Compliance Officer
  - Office of Regulatory Affairs (ORA) - Investigator
- Recent history/lessons learned
  - QbD pilot
  - Expedited/breakthrough submissions

Team Review Process (Previous)

- Kick-off meeting
  - Invite review team, additional experts, reps from OC, ORA
  - Discuss potential product and process risks and review precedence
  - Discuss review deliverables and anticipated timing
- Periodic team meetings
- Team-developed information request (shortly following mid-cycle)
- Review response
- Conduct inspections
  - Reviewer input and more frequent participation
- Finalize review

Conducted in alignment with Good Review Management Practices and PDUFA 5 Deliverables

Team-based IQA (OPQ)

- Team-based Integrated Quality Assessment
  - Maximizes team expertise
  - Provides aligned patient-focused and risk-based drug product quality recommendations
- An IQA team/original NDAs
  - Application technical lead (ATL)
    - Responsible for overseeing the scientific content of the assessment
  - Regulatory business process manager (RBPM)
    - Responsible for process and timeline
  - Discipline reviewers
    - Drug substance, drug product, process, facility, microbiology, biopharmaceutics, and Office of Regulatory Affairs (ORA) investigators.
  - Other members (as needed)
    - FDA laboratories (e.g., Office of Testing and Research), policy, surveillance, and other offices

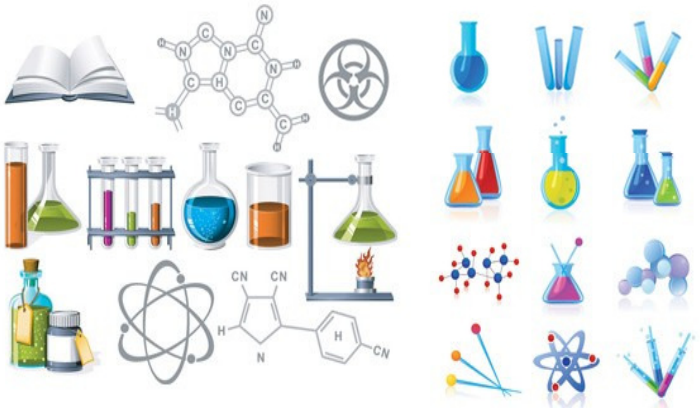
Team Review (NDA) - Observations

- Proactive meeting framework essential to alignment and communication
- Meeting timeframes need to be aligned with PDUFA deliverables (midcycle, LCM, etc)
- Requires appropriate review template
- Effective leadership essential to outcomes and progress
  - One Quality Voice (technical, regulatory)
  - Risk-based conversations (technical)
  - PDUFA deliverables (regulatory)
  - Roles of RBPM and ATL

"Link to the Patient"

Technical

Patient



IQA – Moving Forward

The Office of Pharmaceutical Quality (OPQ) will use a team-based Integrated Quality Assessment (IQA) approach to maximize each team member's expertise and provide aligned patient-focused and risk-based drug product quality recommendations, inclusive of drug substance, drug product, manufacturing, and facilities.

Therefore…

OPQ teams are expected to work in a highly collaborative model
Teams are expected to collaborate effectively within PDUFA timelines
Collaborations/discussions should involve key stakeholders
Communication/discussion of quality risk and link to the patient are critical

IQA Team Roles

Role / Task	Responsible*
Scientific Content / Initial Risk Assessment	ATL
Process and Timeline	RBPM
IQA Executive Summary	ATL / IQA Team
Assessment of Drug Substance	DS/DP Reviewer
Assessment of Drug Product	DP Reviewer
Assessment of the Manufacturing Process	Process Reviewer
Assessment of Facilities	Facility Reviewer
Assessment of Biopharmaceutics	Biopharm Reviewer
Assessment of Microbiology	Micro Reviewer
Assessment of Environmental Analysis	EA reviewer
Labeling & Package Insert	DP Reviewer
Facility Inspections	ORA Leads / SMEs participate
Lifecycle Knowledge Management	ATL/ IQA Team

* Represents General Cases

Patient-Centric 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

Information Requests (NDAs)

- One-directional requests for information during a review
  - Clarification ("Please confirm…")
  - Requests ("Please provide…")
  - Statements of agreement/disagreement/concern
- Allow for official capture and record-keeping for NDA review (sometimes include "request by" date)
- Some options following IRs
  - Clarification tcon with Applicant/follow up dialog
  - Response from Applicant

Information Requests (NDAs)

- Previously, IRs often issued by a single reviewer
- Currently, all NDA IRs issued via team-based approach
  - ATL and RBPM facilitate harmonization of IR language
  - ATL and RBPM also interface with clinical colleagues regarding review status and quality issues
  - IRs often preceded by collective quality team meetings
  - Constant balance between timeliness and number of IRs

Information Requests – Challenges (NDAs)

- Generating meaningful language to effectively convey concerns/clarification needs/deficiencies related to quality
- Capturing sufficient detail to minimize “back and forth” with Applicant
- Including enough background in order to link IR content to patient expectations and/or product performance considerations
- Balancing the above with the need for efficient and concise documentation

Risk Communication - Considerations

- How do we **intentionally** and **explicitly** link the risks identified in our quality assessment to patient outcomes?
  - One Quality Voice

- How do we communicate our findings and recommendations to our stakeholders?
  - Internal: OND, OGD
  - External: e.g., industry, patients

A General Example

- Typical “product quality” language:
  - The manufacturing process is based on bulk addition of propellant during solution compounding instead of incremental propellant addition to the bulk holding tank during the fill run. The assay in-process control shows that assay increases over the fill run. The root cause is propellant evaporation from the bulk holding tank which causes the concentration of the solution to change over time. The applicant should switch to incremental propellant addition to improve assay and content uniformity of the drug product.
- The translation:
  - We cannot ensure that patients will receive similar doses when using different inhalers from the same batch.

End Goal

Patient-Based Assessment

- Product quality assessments that capture important links between product quality and patient outcomes

Communication

- Enhanced interdisciplinary communication throughout the review process
- Product quality recommendations and rationale are clearer to external audiences

ONDP Strategic Priorities (2016-21)

- Enhance the team-based review process
- Proactively support continuous improvement – review quality
- Proactively support continuous improvement – review efficiency
- Facilitate effective, transparent and risk-based communication
- Enhance robust discussions linking quality to clinical performance
- Achieve excellence through a skilled, knowledgeable and collaborative workforce

Linking to the Patient - Considerations

- Focus/align on “Why does it matter to the patient?” or “What is the impact on overall quality?”
- Most effective when discussions are timely, transparent, and robust
- Multiple collaborators often involved (e.g., clinical review division, Applicants, other offices)
- Relies heavily on the content submitted in the application
- Occurs within the appropriate regulatory framework (e.g. PDUFA deliverables, application urgency)
- End result – using sound science and technical expertise to identify/discuss major risks to quality, while communicating effectively regarding necessary mitigation and/or potential impact to the patient

Additional Considerations

- Are we having the right conversation at the right time?
- Determining communication gaps and clarification needs from actual scientific disagreements
- Generating One Quality Voice within the appropriate regulatory framework
- Embracing a “culture of curiosity” (slowing down assumptions)
- Utilizing resources effectively (e.g. combined IRs)
- Building proactive communication into review process
- Considering the audience(s)
- Improving overall risk communication to stakeholders
- “Need for a dialog” = “Need for an IR”?

Conclusions

- Patient/caregiver expectations of quality
  - Safe, effective, high quality, correct identity, perform as labelled, available
- Multiple drivers/values based on risk benefit balance
- Team based IQA currently in use for all NDAs
  - Based on historical team review experience
  - Incorporates risk-based elements in review process
  - Continuously improving based on internal and external feedback
  - Evolving IQA template
- Additional ongoing initiatives
  - Risk communication
  - Clinical relevance (clinically relevant specifications)
- All on behalf of the ultimate stakeholder – the patient

Thank you!

Questions? CDER-OPQ-Inquiries@fda.hhs.gov