CMC Regulatory Review and CGMP Systems in CBER

GMPs By The Sea
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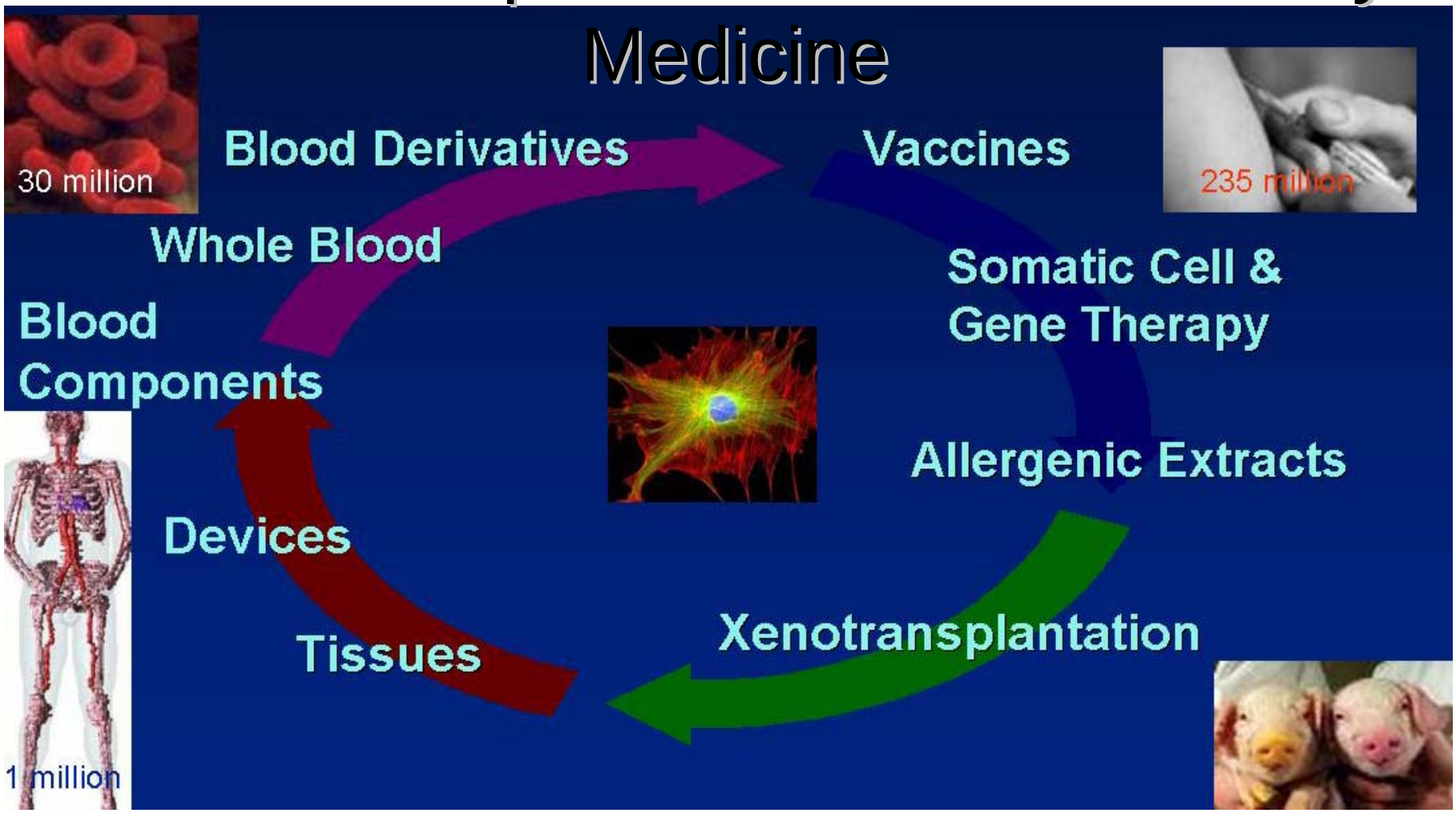
Outline

- Managed Review Process
- Submission (CMC) Review
- Inspections
- On the Horizon

Product Development and Regulation - CBER Philosophy

- **Effective Regulation**
  - Balanced
  - Flexible
  - Responsive
  - Transparent
  - *Predictable*
- **Goal**
  - Protect the public health - individual & collective
  - Assure Safe, Effective and Available products
  - Support product development, foster technological innovation
  - Facilitate product development and product access
- **Influences**
  - Available science, knowledge and understanding
  - Stakeholder input
  - Experience/ Precedent
  - Circumstances

Critical Products for Public Health, National Preparedness & 21st Century Medicine



Managed Review Process

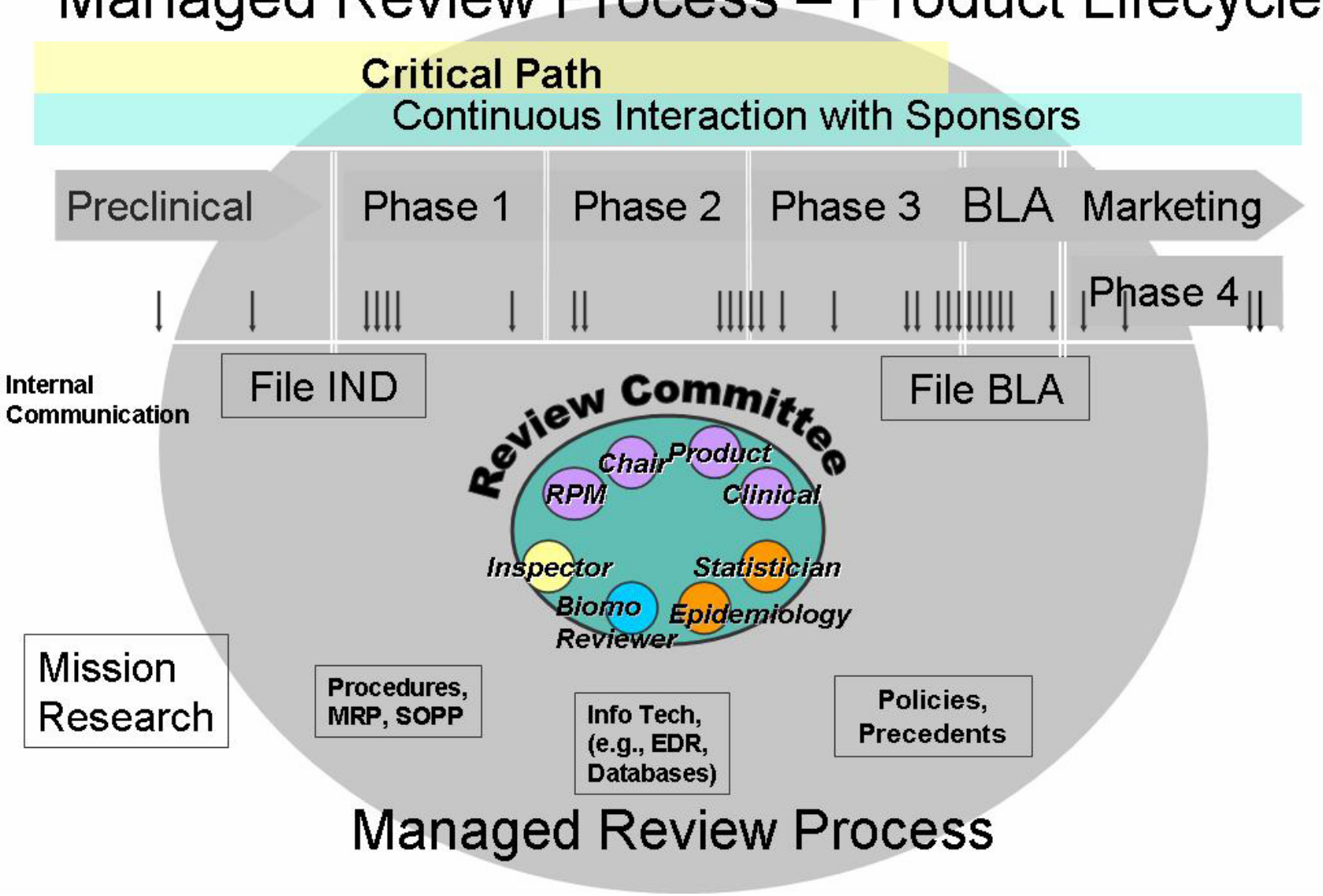
Managed Review Process

- Regulatory Pathways
  - IND/ BLA/ NDA/ ANDA
  - IDE/ PMA/ 510(k)
- With all the different laws, regulations, guidances, SOPPs, databases, PDUFA rules, MDUFMA rules, etc., how can CBER keep it all straight
- ***Managed Review Process*** - Cradle-to-grave approach for the entire regulatory process for investigational and marketing applications for drugs, devices and biologics using SOPPs, guidances, regulations, infrastructure and Laws to govern our processes. (1996)

Review Management

- “Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products,” ***GRMP*** issued April 2005 (CBER/CDER)
- Obligates CBER to GRMP under Good Guidance Practices; deviations only allowed with supervisory approval (only when the specific situation warrants and the justification needs to be documented contemporaneously).
- Consistent with existing CBER Managed Review Process.

Managed Review Process – Product Lifecycle



Review Management Process
Key Elements

- Pre-filing activities, (development)
  - Pre-meetings
- Filing and reviewing submissions
    - Review Teams, process taking regulatory actions
- Postmarketing activities
    - Reports, surveillance, post-approval changes
- Regulatory Research/ Critical Path Research
    - In support of the review process

Examples Managed Review Process Tools

- Process (MRP Manual, SOPPs)
- Action Letter Templates
- Information Technologies
  - Databases
  - Electronic Document Room
    - Review submissions, use review templates*, send correspondence with digital signatures*, etc. (* denotes processes underway)
  - FDA gateway/ Secure e-mail

Product/ Process Control

CMC Review
[21 CFR 610]

CGMP Inspection
[21 CFR 210, 211, 600's]

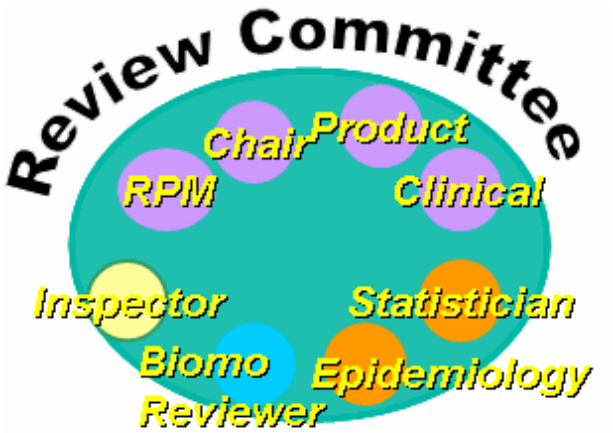
Communication

Submitted ⟷ Companion ⟷ On-site

Source Material
Components
Manufacturing Process
Process Controls
Analytical Procedures/
Specifications
Stability

Validation
Establishment Information

Personnel
Quality Control
Facilities
Equipment
Laboratory Control
Component Control
Production Control
Distribution
Records
Labeling
Validation
Establishment Information



Integration of Review and Inspectional Activities

- CBER has an integrated approach to pre and post market review and inspectional activities
  - Review Committee composed of multidisciplinary reviewers including those with product experience (product reviewer/ product specialist) and reviewers with facility/ GMP experience (inspector reviewers)
  - Inspector reviewers lead pre-license and pre-approval inspections (Supplements) with product specialist
  - Routine post-approval GMP inspections performed by Team Biologics and product specialists.

"It is not a question of how well each process works, the questions is how well they all work together." Lloyd Dobens and Clare Crawford, *Thinking About Quality*

Who Are These Individuals?

- Reviewers – with product expertise (product reviewers/ product specialist)
  - Full-time reviewer or researcher reviewers
    - May conduct active mission-related research
  - Product Offices (OCTGT, OBRR, OVRR)
- Reviewers - with CGMP/ facility expertise (inspector reviewers)
  - Compliance Office (OCBQ;DMPQ)
- Background
  - Biologists, Chemists/ Biochemists, Microbiologists, Immunologists & Others
  - Variety of specific expertise

Scientific/ Product Expertise

- Virology
- Bacteriology
- Parasitic and Unconventional Agents
- Cells, Tissues, and Plasma Biologics
- Manufacturing Technologies
- Emerging Characterization Technologies

Current DMPQ Reviewer Breakdown

- Manufacturing Review Branch 1
  - Bacterial vaccines
  - Allergenics
  - IVDs
  - Gene therapy
  - Plasma derivatives
- Manufacturing Review Branch 2
  - Viral vaccines
  - Cell therapy
  - Blood Grouping Reagents
  - Plasma derivatives

Role of Product Reviewer

- For submission
  - Review CMC information & related (e.g., clinical assays)
  - Serve as product expert on review team
  - Chair BLA Review Committee (for new biologic, manufacturing supplement)
- For inspection
  - Participate as a product specialist in facility inspection (PLI & PAI)
  - Review 483 responses and their section of EIR

Role of Inspector Reviewer

- For Submission
  - Review CMC Information in submission
  - Serve as a GMP/facility expert on review Team
  - Chair BLA Review Committee (for manufacturing supplement)
- For Inspection
  - Determine if inspection is needed
  - Lead for the PLI/ PAI inspection(s) team
  - Review and coordinate team members evaluation of 483 responses - coordinate writing of EIR
  - Provide the recommendation for approval of the establishment for a specific BLA

Submission (CMC) Review

Responsibilities of Review Team

- Review specific sections of the Chemistry Manufacturing, and Controls (CMC) Section of the BLA
  - Identify review issues
  - Identify inspection issues
- CBER SOPP 8401.4 “Review Responsibilities for the CMC Section of Biologic License Applications and Supplements” issued April 8, 2005

Responsibilities of Review Team

- CBER SOPP 8401.4
- Outlines Product Office and DMPQ responsibilities for review and inspectional coverage related to the CMC section
- Designates sections that are primary, shared, review in preparation for inspection or review for general background (FYI)

Responsibilities of Review Team

- “The product offices and DMPQ should review in preparation for the pre-approval/license inspection. These items may be noted as separate issues in a review memo, however the primary means of review will be through documentation in the Establishment Inspection Report”
- EIR becomes part of the approval file

Inspections

Legal Basis For Inspections

- PHS and CFR
  - A biologics license shall not be issued except upon determination that the product and establishment comply with standards established in the BLA and the requirements prescribed in applicable regulations
- FD&C ACT/ PDUFA2
  - An inspection, if needed, is considered to be a part of the complete review of an application
- The role of inspections in CBER's managed review process is based on these laws

Exceptions

- CBER SOPP 8410 “ Determining When Pre-License / PreApproval Inspections are Necessary
  - Limited circumstances when these inspections may be waived, generally limited to pre-approval inspections
  - When inspections are necessary
    - No active U.S. license
    - Time frame of previous inspection
    - Significant cGMP deficiencies during previous inspection
    - Significant manufacturing steps in new areas with different equipment
    - Sufficiently different manufacturing process

Pre-license/ Pre Approval Inspections

- Pre-license
  - Subject to Biologics License Application (BLA)
  - Necessary for licensure under 21 CFR 601.20(d)
    - May be non-U.S. licensed firm
    - May be U.S. licensed firm with a new product under BLA
- Pre Approval
  - Subject to Prior Approval Supplement under 21 CFR 601.12(b)
    - May be new manufacturing facility
    - May be contract manufacturing facility
    - May be significant process changes

Pre-license/Pre-approval Inspection Team

- Division of Manufacturing and Product Quality, OCBQ/CBER – lead inspector
- CBER product division from OBRR, OVRR, or OCTGT – product specialist
- ORA District Office or headquarters (foreign) informed of inspection and participation requested
  - Team Biologics investigator participation ideal for “life cycle” approach

During the PLI/PAI

- Product reviewers
  - Focus on process/product control limits (including viral/ impurity clearance, where appropriate), assays and product specifications, process control
- Inspector reviewers
  - Determine facility compliance w CGMP 210, 211 & additional stds 600's
  - Focuses on bioburden/ endotoxin controls, cleaning and hold times, aseptic and sterilization process, and utility systems data verification
- All
  - Verify information and data
  - Thoroughly assess protocols and other deviations

Process Validation: Review and Inspectional

- Review
  - Currently, in addition to the product development information and data submitted and reviewed under the IND, process, assay and system validation protocols and data summaries are submitted and reviewed under the BLA or BLS
- Inspection
  - Evaluate the complete qualification/ validation information, raw data, developmental data

CGMP Inspection Team

- Team Biologics member(s) – lead investigator and other GMP investigators
- Product specialist(s) from Product Division (OBRR, OVRR,OCTGT)
  - May be more than one depending on products produced
  - May participate “off-site”
- OCBQ personnel might also be contacted by the investigator(s) during the inspection

Compliance Program for Biological Drugs 7345.848

- Systems-based approach for biological drugs was implemented in December 2004
- Goal to reduce resource investment by FDA and industry while maintaining safe and effective biological drug products
- Annual evaluation was developed to assess whether goals have been met
- http://www.fda.gov/cber/cpg/cpg.htm

Post Approval CGMP Inspections

- Review of defined systems based on established levels – Level I or Level II
- Product specific review also performed
- Includes assessment of changes made since last inspection
  - Submitted properly?
  - Validated adequately, when applicable?
- Includes follow-up on Biological Product Deviation Reports
- May include follow-up on other information received e.g. complaints

Interaction with Other Agency Groups

- Team Biologics
  - Daily Interactions
  - Operations Group
  - Joint training activities
  - Work w/ Pharmaceutical Inspectorate
- ORA
  - Biological Product Committee
  - Biologics Cadre – Tissue and Blood Investigators – regular cadre calls
  - Tissue and Blood Inspection Teams
  - Training
    - PAT Training CBER product reviewers and inspector reviewers are participating in Agency training
- CDER & CDRH Office of Compliance, CPQ

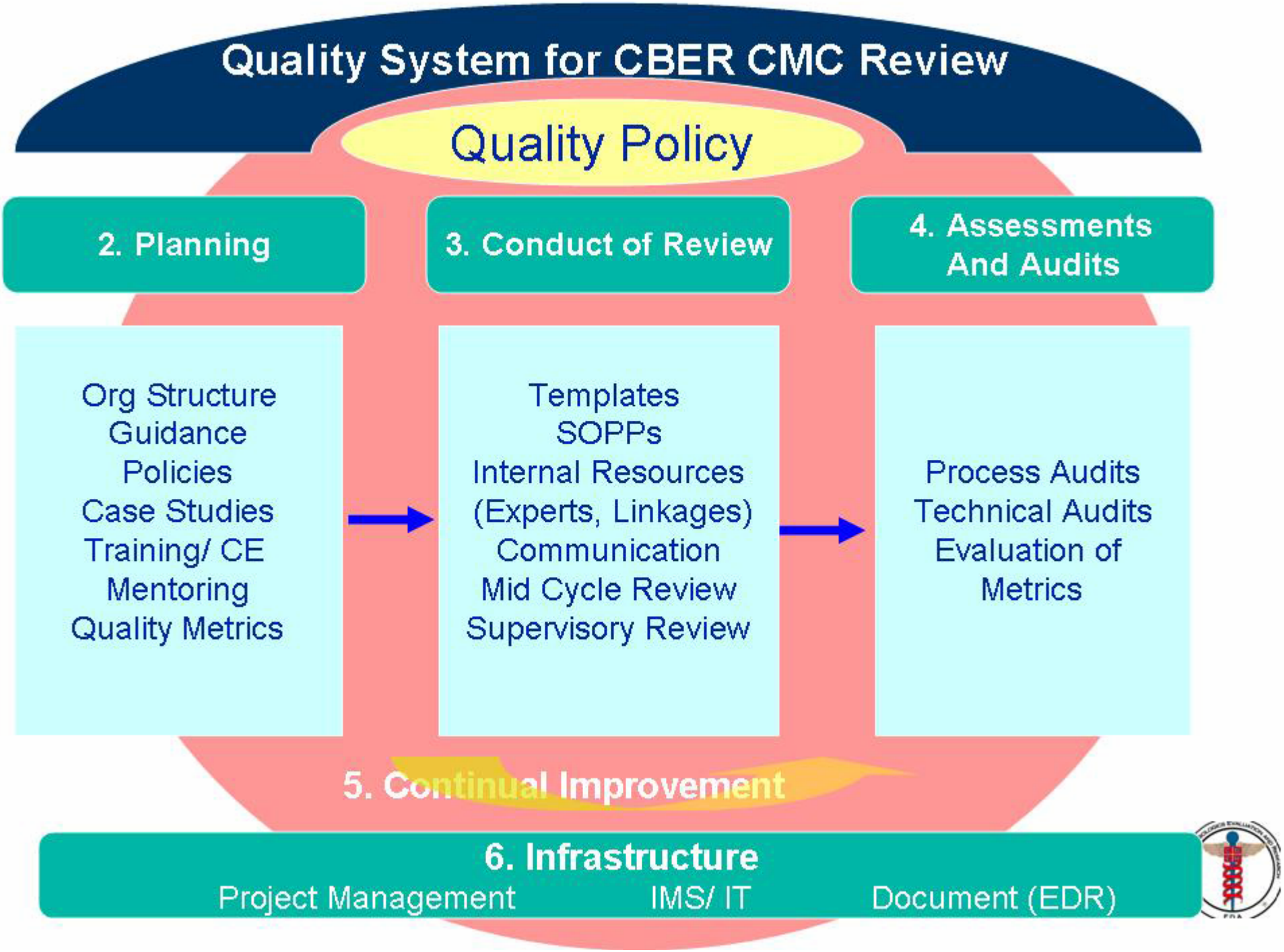
Integration of CBER

- Integration of OCBQ, inspector reviewers &, product reviewers and other disciplines
  - Rule/ regulation/ guidance development
  - Coordinating committees, (CMCCC, RMCC, SMCC PCC), Safety teams
  - Joint training – regulatory, technical/ scientific, other

On The Horizon

Potential Impact Topics

- Q8 Quality By Design
- Q9 Quality Risk Management
- Q10 Quality Systems
- Process Analytical Technologies
- Post Approval Changes - Supplements
- External Standards Development
- Quality Systems - CMC

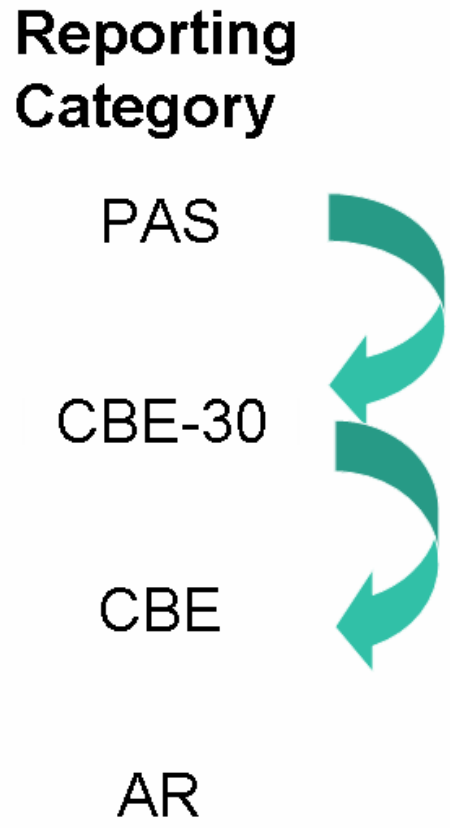

Quality System for CBER CMC Review
Quality Policy
2. Planning
3. Conduct of Review
4. Assessments And Audits
Org Structure
Guidance
Policies
Case Studies
Training/ CE
Mentoring
Quality Metrics
Templates
SOPPs
Internal Resources
(Experts, Linkages)
Communication
Mid Cycle Review
Supervisory Review
Process Audits
Technical Audits
Evaluation of Metrics
5. Continual Improvement
6. Infrastructure
Project Management
IMS/ IT
Document (EDR)

Risk Management

- Formalization of Risk Management
- Training in Risk Management
- Evaluation of Risk Assessment for CMC issues
  - Variable Approaches
  - Discussion of risk assessments provided to date
  - How to assess product and process?
  - Structural (organizational) and communication tool

Reporting Post Approval Change

- Existing System provides great flexibility
  - Based upon Potential
  - substantial, moderate, minimal
- Currently revising guidance on “Specified Products” and Biological Products
  - Better clarification on examples
  - Risk – based approach
- Encourage use of Comparability Protocols
  - More user-friendly
- Considering proposed regulation changes in light of 21CFR 314.70



Conclusions

- Early and continued interactions with sponsors/ manufacturers and integration of review and CGMP issues has proven beneficial, particularly when **complex and/or innovative technologies** are proposed in facilitating product development and improvement
- Effective Interaction
  - Scientific foundation will need to be established and effectively communicated among individuals of different scientific background
  - Risk will have to be appropriately assessed
  - Quality will need appropriate oversight
- Opportunity to meet future needs
  - Increasing complexity (e.g., complex drugs, drug delivery systems, nanotechnology, biotechnology, drug-device – cellular-tissue combinations, etc.) and anticipated need for patient customization

Conclusions

- The team approach to CMC review and pre-and post-approval inspections has been extremely valuable by:
  - Facilitating better communication, understanding of issues, consistency
  - Facilitating preparation for inspection - specific product and process knowledge and issues
  - **Providing a shared understanding between reviewers, inspectors and investigators of biological drug product manufacturing and application of CGMP requirements**

- Product reviewer/ product specialist input allows for better assessment of product specific issues and potential product impact
  - Real-time input - on inspection
  - Other situations - Adverse Event Evaluation
- Effective Management and Integration of the review and inspection process is critical to success.

Conclusions

- What can Industry do to facilitate the review and inspection process?
  - Early and continued communication with FDA through the product life cycle is key
    - CBER SOPP 8101.1 “Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants” ‘http://www.fda.gov/cber/regsopp/81011.htm
  - No surprises, electronically facilitated, high quality submissions
- Acknowledgements – CBER/FDA staff especially Mary Malarkey, Laurie Norwood
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