



Biotechnology Products

CASA/FDA

Pharmaceutical Industry Seminar

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Outline

- Regulatory authority
- Biotechnology Product Quality Review
 - Biological License Application (BLA)
- Microbiology Product Quality Assessments
 - Review issues
- Pre-license Inspections
 - Inspection issues
- Conclusions



Regulatory Authority

Current Laws

- Public Health Service Act
 - Section 351 (a)(2)(C) -- Licensure of biological establishments and products
 - The **biological product must be safe, pure and potent**
 - The **facility** in which the biological product is manufactured, processed, packed, or held **must meet standards designed to assure that the biological product continues to be safe, pure and potent**

- Federal Food, Drug, and Cosmetic (FD&C) Act (1938, 1962, 1997, 2007)
 - Interprets that “biological products” are also “drugs”
 - The FFD&CA applies to a biological product, except no application required under section 505
 - Inspection under both the provisions of both the PHS Act and the FD&C Act

Biologics Regulations

21 CFR Part 600-680

- 21 CFR 601.2 describes the “specified” biologics
 - Therapeutic recombinant DNA-derived products (some in CBER)
 - Monoclonal antibody products for in vivo use
 - Therapeutic synthetic peptide products of 40 amino acids or less (regulated in CBER)
 - Therapeutic DNA plasmid products (regulated in CBER)
- TRP and MAB are “specified” biologics regulated by CDER (since 2003)
- Some of the 600 regulations do not apply to the specified biologics [600.10(b) and (c), 600.11, 600.12, 600.13, 610.11, 610.53, 610.62]

21 CFR 601.2 - Applications for biologics licenses

- (a) *General.* To obtain a biologics license...the manufacturer shall **submit an application**...
...and the **address of each location** involved in the manufacture of the biological product shall be listed in the biologics license application
- (d) Approval of a biologics license application or issuance of a biologics license shall constitute a determination the **establishment(s)** and the **product** meet applicable requirements to ensure the continued safety, purity, and potency of such product.

21 CFR 601.20 – Biologics licenses; issuance and conditions

- 601.20 (a) *Examination - compliance with requirements*
 - Biologics license approved **only upon examination of the product and upon a determination that the product complies with the standards** established in the biological license application and the requirements prescribed in the regulations in this chapter including but not limited to the **good manufacturing practice requirements** set forth in parts 210, 211, 600, ...

21 CFR 601.20 – Biologics licenses; issuance and conditions (cont.)

- *(d) Inspection - compliance with requirements*
 - BLA approved only after inspection of the establishment(s) listed in the BLA
 - upon a determination **that the establishment(s) complies** with the standards established in the BLA and the requirements prescribed in the regulations
- *(e) One biologics license to cover all locations*
 - **One license to cover all locations** meeting establishment standards in the approved BLA
 - Each location is subject to inspection by FDA



Biotechnology Product Quality Review of Biological License Application (BLA)

Pharmaceutical CGMP for the 21st Century - A Risk Based Approach

- Initiative launched in 2002
 - To ensure that “the product review program and the inspection program operate in a coordinated and synergistic manner.”
 - Intended to encourage the adoption of modern and innovative manufacturing technologies
 - Overarching philosophy is:
 - ***Quality should be built into the product, and testing alone cannot be relied on to ensure product quality.***

Modernization for the Desired State: Integration of Functions

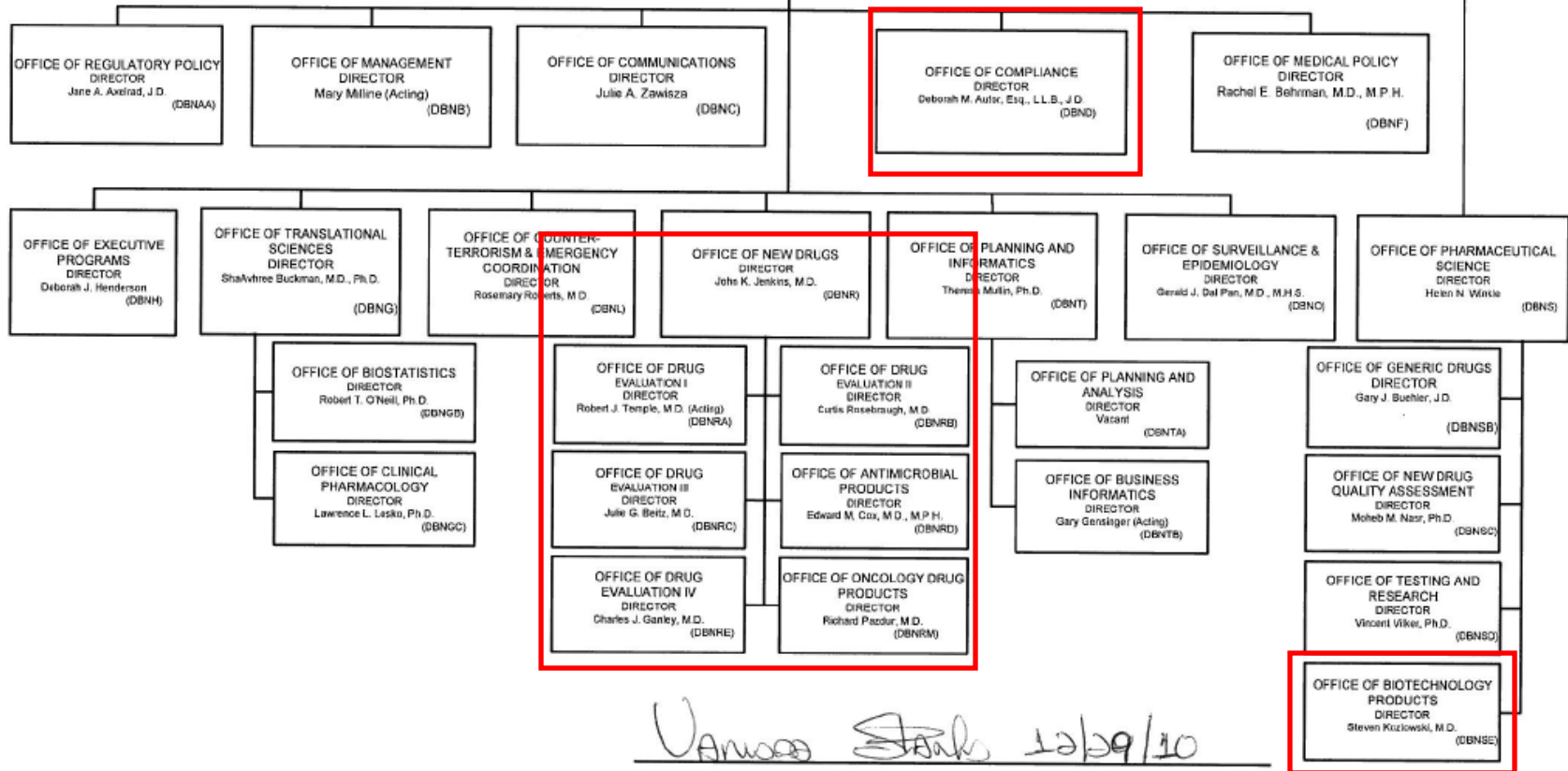
- Industry
 - R&D and Production need to be integrated
 - Modern quality systems are needed domestically and internationally
- FDA
 - **CMC and cGMP Programs need to be integrated**
- Will lead to Industry and Regulator synergy to advance to the desire state

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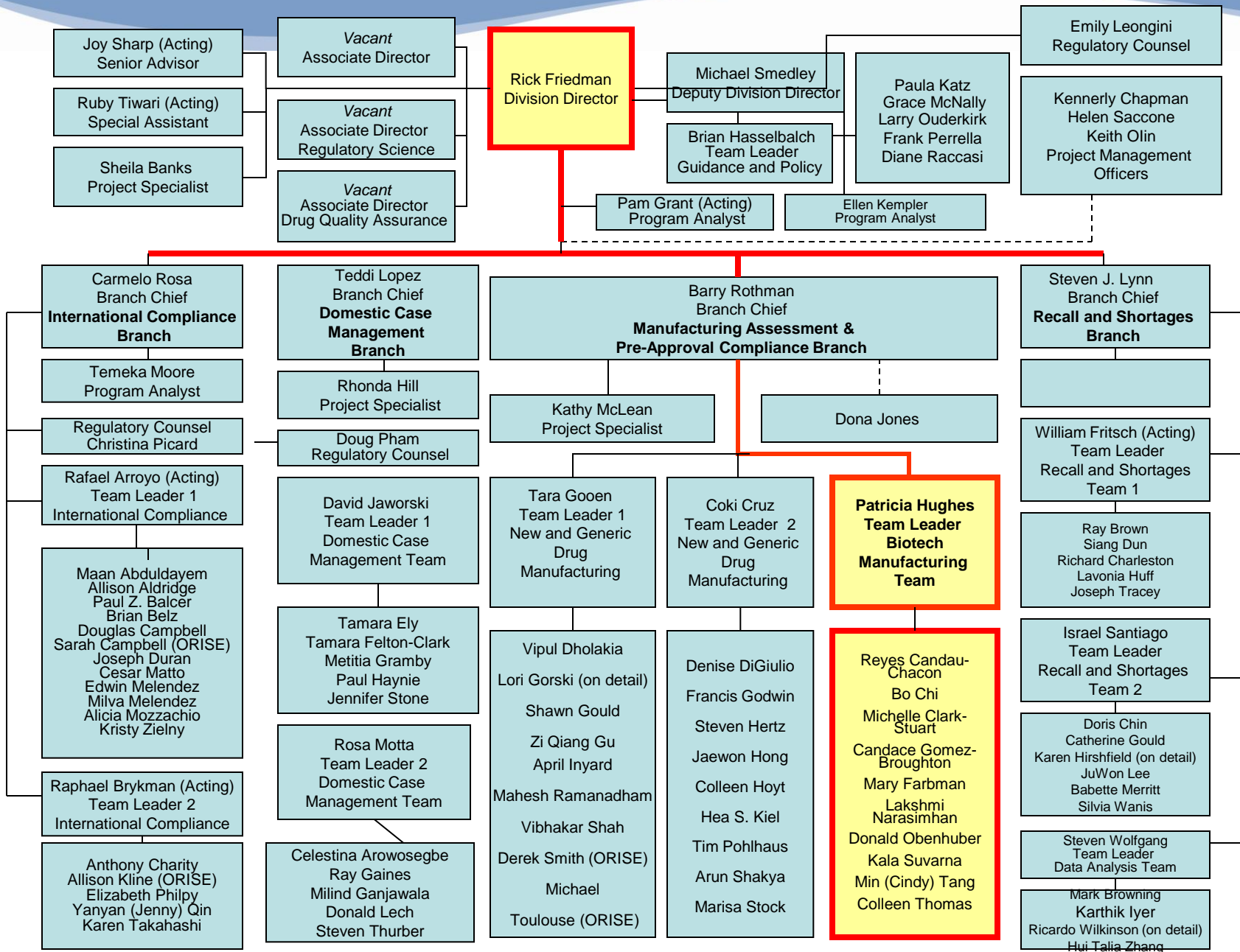
Vanessa Stark 12/29/10

Approved by the FDA Reorganization Coordinator and
Principal Delegation Control Officer



Division of Manufacturing and Product Quality (DMPQ)

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Integrated Review and Inspections for BLAs and Supplements for Biotech Products

- Review and inspection responsibilities are shared between Office of Biotechnology Products (OBP) and Office of Compliance (OC) (Biotech Manufacturing Team [BMT])
 - New Manual of Policies and Procedures (MAPP 4730.3): Issued in 2009
 - Team approach to review and inspections
 - Enables a continuum in the regulatory process from review and inspection
 - Allows for a better assessment of the firm's process understanding and quality oversight

Integrated Review and Inspection

- OBP
 - **Leads in the overall assessment for product quality:**
approves manufacturing process and final specifications (except microbiology)
 - Active participant on inspection
 - Product specific elements, data verification, conformance to standards and commitments in the BLA or supplement
- BMT
 - Provides a microbiology assessment of drug substance and drug product sections of the applications and supplements:
 - Approves manufacturing microbial control strategy and drug substance and drug product release criteria for microbiological specification, assess cross contamination controls
 - **Leads the inspection team**
 - Responsible for evaluating cGMP compliance status of a firm and conformance and commitments in the BLA or supplement

Overall Responsibilities of BMT and OBP

- OBP
 - Product characterization
 - Impurity profile
 - Final test results (except microbial)
 - In-process tests (except microbial)
 - Test methods/validation
 - Raw material sources
 - Manufacturing process design (except for microbial control and sterility assurance)
 - Cell lines
 - Viral reduction/inactivation
 - Reference standards
 - Stability program
- BMT
 - Facility design
 - Equipment qualification
 - Manufacturing process execution
 - Equipment sterilization
 - Bioburden control
 - Sterile filtration
 - Cleaning
 - Depyrogenation
 - Aseptic processing
 - Media Fills
 - HVAC/EM
 - Water systems
 - Visual inspection
 - Lyophilization
 - Computers systems



Microbiology Product Quality Assessments

Important FDA Guidances for Microbial Control

- FDA Guidance for Industry 1994, “Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.”
- FDA Guidance for Industry 2004, “Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice.”
- FDA Guidance for Industry 2006, “Quality Systems Approach to Pharmaceutical CGMP Regulations.”
- Other ICH Guidances: ICH Q6B, Q7, Q8, Q9
- CDER MAPP: [5040.1 \(PDF - 145KB\) Product Quality Microbiology Information in the Common Technical Document - Quality \(CTD-Q\)99](#)
(Issued 5/24/2004)

ICH Q6B: Key Concepts on Microbial Control

- Manufacturing processes should be designed to limit microbial contamination / proliferation in non sterile process intermediates
 - In-process testing should be conducted at critical decision making steps (e.g. end of cell culture process)

- Manufacturing process must be able to produce a sterile product with a high degree of assurance
 - Some processes are intended to produce a sterile bulk drug substance
 - Finished biotech drug products are sterile

Susceptibility to Microbial Contamination

- Biotech processes and products are prone to microbial contamination because,
 - Products are heat labile and cannot be terminally sterilized
 - Raw materials, personnel and the manufacturing environment are a source of bioburden
 - Products, process intermediates and raw materials support microbial growth

Elements of a Microbial Control Strategy

- Facilities including utilities: design suitable for the intended use
 - Qualified, maintained and monitored
 - Controlled classified areas; appropriate segregation of areas
- Equipment: qualified and maintained in a state suitable for microbial control
 - Appropriate qualification for the intended use
- Raw materials: tested and screened for microbial quality
 - Appropriate raw material quality for the intended use
- Processes: designed and validated for microbial control
 - Eliminate bioburden at critical steps in the process
 - Minimize hold steps and personnel interactions
 - Use of closed systems, when possible
 - Validate critical manufacturing and hold steps for microbial control

Microbiology Product Quality Review of a BLA: Drug Substance (API)

- Manufacturing microbial controls
- Qualification of in-process and release microbial methods
- Media and buffers
- Column cleaning/sanitization/storage
- Shipping validation
- Release of bulk drug substance
- Cross contamination controls

Drug Substance Review: Some Specifics

- Evidence of monitoring of bioburden and endotoxin levels at critical manufacturing steps using qualified bioburden and endotoxin tests
 - Bioburden and endotoxin limits
- Microbial control of media and buffers
 - Preparation, use and storage conditions at scale
 - Microbial and cross contamination controls, monitoring, storage conditions
 - Bioburden and endotoxin limits
- Validation of in-process/product intermediate hold times at manufacturing scale
 - Specified hold conditions with established bioburden and endotoxin limits
- Validation column resin and lifetime use
 - Microbial control with established limits
 - At scale

Drug Substance Review: More specifics (cont.)

- Evidence of microbial control during the manufacture of conformance lots
 - Bioburden and endotoxin data from conformance lots
- Shipping validation data under worst case conditions
 - Scale down studies / simulations
 - Actual temperature control data from shipping runs
- Drug substance bioburden and endotoxin release specifications

Microbial Control Strategy for Cell Culture

- Culture purity must be maintained throughout the inoculation, seed expansion and production operations.
 - Ingress of contaminating adventitious agents must be prevented
 - Open operations should be conducted using aseptic processing methods and in controlled areas
 - Closed systems should be used where possible
 - Sterilization cycles for the sterilization of media and equipment should be validated
 - Special attention should be given to the screening and sterilization of media components from biological sources
 - Media simulations in bioreactors and hold vessels may identify equipment problems

Microbial Control Strategy for Purification

- In process purification intermediates (column eluates, pre-UF/DF intermediates)
 - Typically filtered through 0.2 micron filters
 - to protect the column resins from colonization with bioburden
 - to prevent proliferation of bioburden during processing steps and hold conditions
 - Bioburden monitoring
 - Bioburden limits (typically range 10-1000CFU/10mL)
- In process purification intermediates hold conditions should be validated microbiologically at scale
 - Establish maximum hold times

Microbial Control Strategy for Purification (cont.)

- Column resins and membranes from UF/DF systems should be cleaned, sanitized after each use
 - Procedures should be effective in controlling bioburden and endotoxin.
 - Resins should be used only within the validated use time.
 - Resins and membrane should be stored under conditions that do not promote microbial growth

Microbial Control Strategy for Filtration of the Formulated Bulk Drug Substance

- The final filtration step in a drug substance manufacturing process is often a bioburden reduction step intended to reduce bioburden load
 - Filters should be integrity tested
 - Operations conducted in controlled classified environments

Microbial Control Strategy for Filling of Formulated Bulk Drug Substance

- After filtration bulks may be filled into stainless steel vessels, bottles or sterile bioprocessing bags
 - Liquid Bulks – that is bulk to be stored at 2-8 C
 - The fill process may occur using aseptic processing conditions in an ISO 5/6 area
 - The environment and personnel should be monitored
 - Containers/closures should be cleaned and sterilized using validated cycles
 - The aseptic operations should be qualified in media simulation studies
 - The suitability of the container closure should be demonstrated
 - Frozen bulks – to be stored frozen at -20 to - 60 C
 - The fill process may occur in an ISO 7/8 area when all operations are closed
 - Containers/closures should be cleaned and sterilized using validated cycles
 - The suitability of the container closure should be demonstrated

Summary of Expectations for Microbial Control: Drug Substance

- In-process bioburden limits typically range from 10-1000 CFU/10 mL.
 - Limits should be based on product impact, manufacturing capability and the ability of the material to support microbial growth
 - Tighter limits are expected for higher-risk steps and for steps that are closer to the end of the process
 - Validation of hold steps within the process is required to demonstrate control of the process and to set time limits
 - Routine monitoring is required to show ongoing control
 - Ongoing monitoring is required because equipment or cleaning/sterilization may malfunction with respect to bioburden levels

Microbiology Product Quality Review of a BLA: Drug Product

Microbial control, sterility assurance and microbial product quality attributes

- Microbial attributes e.g., container closure integrity as it relates to product sterility
- In-process controls and hold limits
- Sterile filtration - filter validation
- Sterilization and depyrogenation validation of sterile product – contact equipment and components and equipment re-qualification program

Microbiology Product Quality Review of a BLA: Drug Product (cont.)

Microbial control, sterility assurance and microbial product quality attributes (cont.)

- Media fill program
- Environmental monitoring
- Lyophilization
- Microbial specifications for release and stability (sterility, bioburden, endotoxin, container-closure integrity, reconstitution conditions, etc.)
- Shipping validation



Pre-License Inspections

Types of Inspections

- Pre-license (PLI) - announced, generally required for approval of an original BLA or an unlicensed manufacturing facility
 - Manufacturing and testing sites are subject to inspection by CDER
 - Other associated establishments listed in the BLA are covered by district inspectors
- Pre-approval (PAI) – announced, could be waived
 - Triggered by major changes as described in certain Prior Approval Supplements involving changes that have a substantial potential to have an adverse effect on the identity, strength, quality and purity or potency of the product (21 CFR 601.12)
- Surveillance (biennial, post-licensure) – announced or unannounced
 - District with CDER product reviewer participation
- For cause inspections
- IND clinical materials manufacturers
 - No formal inspection requirement for sites manufacturing biologics under clinical investigation
 - For cause inspections
 - Inspection may be triggered by Treatment IND protocols

Purpose of a Pre-license Inspection

- To meet statutory obligation in FD&C and PHS Acts
- To assess compliance with CGMPs and applicable sections of the 21 CFR 600 and 21 CFR 210 and 211
- To verify compliance with commitments made in the BLA or supplement

Pre-License Inspections

- Led by OC/DMPQ/BMT
- District invited to participate (on domestic inspections)
- Inspections are announced and scheduled when manufacturing operations can be observed.
- Both BMT and OBP inspectors should verify compliance with commitments in the BLA and audit the authenticity of the submitted data and assess overall compliance with CGMPs.

Key Guidances and Compliance Programs

- For drug substance:
 - CP 7356.002M Inspections of Licensed Biological Therapeutic Drug Products
 - CP 7346.832, Pre-approval Inspections
- For finished drug product:
 - 7356.002, Drug Manufacturing Inspections
 - 7356.002A, Sterile Drug Process Inspections
 - 7356.002M, Inspections of Licensed Biological Therapeutic Drug Products
 - CP 7346.832, Pre-approval Inspections
 - Aseptic Processing Guidance 2004
- For all CPGMs: http://intranet.ora.fda.gov/directives/cpgm/master_list.htm

Compliance Program 7346.832

- Applies to all drugs
 - Risk-based decision criteria for performing an on-site inspection with consideration for public health impact
 - Contains concepts of modern product assessment system
 - Sets the stage for a pre-approval inspection program that reflects a manufacturer's understanding of the product and its manufacturing process
 - **Shift responsibility to a manufacturer's quality system** to evaluate changes to the manufacturing operations through the use on internal change control systems.

CP 7356.002M Inspections of Licensed Biological Therapeutic Drug Products

-”Ensure therapeutic drug products are manufactured in compliance with current Good Manufacturing Practice regulations and they comply with standards and commitments made in the license applications and / or supplements”.

PROGRAM 7356.002M

Inspection Coverage

1. Components
 - a. Master Cell Bank (MCB) and Working Cell Bank (WCB)
 - b. Media, Buffers
 - c. Containers/closures
2. Manufacturing
 - a. Aseptic/controlled process
 - b. Endotoxin levels
 - c. Fermentation/Bioreactors
 - d. Disruption and Harvest
 - e. Purification
 - f. Viral inactivation/removal
 - g. Lyophilization
3. Validation
 - a. Process
 - b. Computer
 - c. Shipping
4. Testing and Laboratory Controls
5. Environmental controls/monitoring
6. Cross contamination
7. Non-conforming product
 - a. Investigation
 - b. Reworking/reprocessing
 - c. Complaints
 - d. Recalls
 - e. Product deviations
 - f. Adverse Experience Reports
8. Changes to be reported

PROGRAM 7356.002M

Inspection Coverage (cont.)

9. GMP

- a. Equipment
- b. Buildings
- c. Quality Control
- d. Personnel/Training
- e. Waste processing
- f. Labeling/packaging

10. Records

- a. Mater Production
- b. Batch Records
- c. Distribution
- d. Stability

11. Lot release

Inspection Strategy

All systems covered, as applicable

- Quality
- Facilities and Equipment
- Production
- Materials
- Laboratory Controls
- Packaging and Labeling

Inspection outcome

- No action indicated (NAI)
 - Form FDA 483 not issued, EIR written
- Voluntary action indicated (VAI)
 - Form FDA 483 issued
 - Responsible person must respond regarding observations
- Non-concur approval
 - Non approval of BLA or supplement
 - Manufacturer has opportunity to correct

Inspection Close out

- A response to 483 observations is required in order to receive BLA approval and licensing
- Response to 483 observations should be sent within 15 business days
- In CDER, an OC/DMPQ compliance officer is assigned to assess the adequacy of the responses to 483 observations
 - The compliance officer
 - From the NGDMT team (domestic) or from the International Compliance Branch (foreign)
 - Is not a reviewer of the application
 - Is responsible for providing a recommendation for approval of the application based on a review of the 483 observations, the EIR and the responses from the firm



Inspection issues

Quality Oversight

- Inadequate quality oversight
 - Drug substance batches with high bioburden counts released
 - Batches that exceeded validated parameter ranges upstream and were processed downstream
- Record control is inadequate.
 - Batch records for buffer, media lost and not reviewed or approved by QA.

SOPs

- SOPs are not executed consistently for the management of deviations, change control, laboratory records, and logbooks.
- Numerous deviations due to SOPs withdrawn & newer version not available at different areas of the facility.

Facility

- Pest control issues
 - Alert and action limits for clean rooms
- Not clean and well-maintained facilities
- Environmental monitoring issues (mold, etc.)
- Utility areas found in disrepair (corrosion, leaking pipes, diagrams not updated after changes)

Recent facility problems discovered during in a Biotech firm

- Roof leaks in bioreactor and supporting rooms
 - EM excursions with *Penicillium* species in gowning airlocks, media prep suites
 - Bioreactor contamination in several harvest lots with *Penicillium* spp. and *Bacillus lentus*
 - No evaluation of the effectiveness cleaning and sanitizing methods are effective against the *Penicillium* spp. Isolated during routine EM monitoring from 2008 -2010.

Utilities

- High bioburden counts for water used as final rinse for equipment cleaning
- No monitoring of process gases

Equipment

- Deficient equipment qualification and requalification
 - Incorrect installation of components, valves, sampling devices, slope of condensate lines
 - Leading to contaminated bioreactor runs
- Ineffective preventive maintenance program for manufacturing equipment
 - Large number of process deviations (including bioburden control) due to equipment failures
- Inadequate validation of dirty, clean, sterile hold times
 - Involving equipment, e.g., bioreactors, purification vessels, UF/DF membranes systems, formulated bulk drug substance storage vessels, etc.
 - Bioburden and biofilm problems
 - Faulty drain design

Production

- Discrepancies between manufacturing process described in the BLA and batch records
- Inadequate aseptic methods observed during formulated bulk filtration
- Hold times for purification in-process intermediates not validated
- Re-use of column resins not qualified
- UF/DF membrane lifetime not established

Production (cont.)

- Lack of process understanding leading to significant adjustments after process validation and inconsistent yields
- Incomplete process validation
 - Addition of process control parameters, modifications to set points, changes to process design after “validation”
- Inadequate microbial control leading to over action limits and discarded lots
- Resin and UF/DF lifetime not monitored for microbial control
- Inadequate management of buffer and product-contact hoses

Materials

- Validated expiration or use-by dates for critical raw materials not supported by data
 - cell culture medium
- Materials not appropriately segregated
 - quarantined, released, etc.

Laboratory

- Assays not appropriate for their intended purpose and/or not qualified
- Laboratory records for the potency assay lack sufficient detail
 - Do not cross reference appropriate procedures to ensure consistent method execution
 - Do not describe all steps
- Inappropriate handling and storage of the reference standard

Conclusions

- Regulatory oversight of BLA applications involves a product quality assessment and establishment inspections
 - Performed by both reviewer/inspectors from OBP and OC (BMT)
 - Integrated regulatory oversight for product quality
 - CMC standards and CGMPs
 - Coordination of multidisciplinary functions
 - Product and establishment expertise
- Should lead to
 - More consist process and product and ensure product quality
 - Post-approval surveillance program should continue to provide a strong regulatory oversight, ensure manufacturing practices are current and provide feed back to the pre-approval regulatory oversight program.

Acknowledgements

- Kalavati Suvarna, Ph.D.
- Anastasia Lolas, M.S.
- Bo Chi, Ph.D.

Recent publications

- Suvarna, K. et al., (2011) Case Studies of Microbial Contamination in Biologic Product Manufacturing, *American Pharmaceutical Review*, Jan-Feb, 50-56
- Lolas, A. and Metcalfe J., (2011) Evaluation of the Microbial Growth Potential of Pharmaceutical Drug Products and Quality by Design, *PDA J. Pharm. Sci. and Tech.*, Vol. 65 (1), 63-70
- Lolas, A. et al., (2010) CMC Microbiology Review of Biologics License Applications and Pre-approval/Pre-license Inspections: Therapeutic Biological Proteins, *American Pharmaceutical Review*, March/April 2010, 56-60.