CBER Perspective

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Food and Drug Administration

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

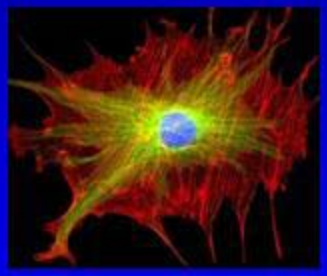
Blood Derivatives

Vaccines

Whole Blood

Somatic Cell & Gene Therapy

Blood Components



Allergenic Extracts

Devices

Xenotransplantation

Tissues

CBER's Biological Products: Unique Issues

- Broad range of product types and manufacturing technologies
- Complexity of manufacturing facilities/materials, processes and products
  - Often difficult to characterize, need for extensive process controls, product and intermediate testing, personalized medicine
  - Made using, derived from or are living cells, organisms or tissues
  - Multiple mechanisms of action (not always predictable)
- New technologies and products – high visibility/interest, complex risks
- Highest public concern for safety of critical products often given to healthy individuals – vaccines (235 million), blood (30 mill), tissues (>1 mill)
- Unique roles in health care and national preparedness (pandemic, war/disaster, counterterrorism)
- Market incentives and, as a result, infrastructure, frequently weak for preventive measures, emerging technologies and diseases, including many orphan and sole source products

Major 2007 – (2008) Initiatives

- Pandemic/emerging threat preparedness
- Enhanced product safety: interdisciplinary safety teams + new approaches to data
- Improve manufacturing and product quality
- Product testing and assay development organization, laboratories & quality initiative
- Innovative, safe, and effective products to patients – including Tissue Engineering Team, Critical Path, Research Management
- Strengthening human and organizational resources
- Global harmonization and collaboration
- PDUFA and FDARA

CBER's Safety Teams

- Tissue (2004), Blood (2006), Vaccine (2007)
  - Multidisciplinary and collaborative – each includes product, manufacturing, safety, clinical, compliance, and communication experts – all share common data
  - Meet at least monthly, IOD participates, entire team also meets quarterly with Center Director/Deputy – can be immediately convened in any emerging/urgent situation
  - Structured interfaces with ORA, CDC, others as appropriate
- Goals/accomplishments:
  - Proactively and rapidly identify and address significant ongoing and emergent safety issues
  - Serve as focus for developing and implementing longer term priorities, innovative practices and collaborations, and quality improvement
  - Enhance internal and external communication and collaboration (including public, rest of FDA, CDC, HRSA, international/WHO etc.)

Elements of QBD/ Quality Initiatives

ICH / non-ICH topics

Includes Submission, review and inspection

"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*

QBD and Benefits

- Successful Application of QBD and resulting benefits (regulatory flexibility) depend upon:
  - Systematic Approach
  - Level of scientific understanding, process and product knowledge developed
    - Biotech and biologics includes
    - Understanding the mechanism of action both in terms of efficacy and safety
    - Knowledge of quality attributes of the drug substance and their impact on safety and efficacy and product performance
      - Knowledge how impurities impact Q, S and E
      - Knowledge how formulation impacts product quality
  - Design Space – determining multidimensional combinations and interactions of variables to provide an assurance of quality
  - Risk Assessment & capability of process control strategies to prevent or mitigate risk
  - Internal Quality Systems

Implications For CBER-Regulated Products

- *Historically "The process is the product"*
  - Nature of product influenced this approach
  - For many biologics, relationship to safety and efficacy is shown directly through clinical studies with tight linkage to process, process controls and specifications for lots used in clinical studies
- Advances in analytical and manufacturing technologies, better characterization, process and product understanding led to increased regulatory relief in some areas - "specified products"

Is There Something Really New Here?

- Yes and No
- Required to establish control of process
- CBER emphasized ***"Know thy process and thy product"***
- Elements of QBD (and PAT) have been practiced by manufacturer of biotech and biologics products
  - Biologics and biotechnology by their nature necessitate better understanding for control and consistent production
  - QBD similar to lifecycle approach to process validation advocated by CBER as means of process control
  - Risk Assessments have been conducted and used
- However, potential opportunity for:
  - Better process and product understanding,
  - Application of new technologies & process control
  - Better understanding and communication of risk
  - Facilitated change management

Relative Relationship Among Products

- Product Characterization
- Identification/ selection of critical quality attributes
- Relationship of quality attributes to efficacy and safety
- Relationship of process control to quality attributes

Naturally-Derived (Trad. & Novel Biologics)

Recombinant Biologics

Synthetic

Potential for Application of QBD

Selective Application of Quality Initiative Elements

- Even in absence of QBD,
  - Risk management can still be applied to some areas of review and manufacturing (facilities)
  - Quality Systems can be developed or strengthened
    - Establish a state of control, based upon modern Quality System principles, to ensure the consistent production of high quality, safe and efficacious product
    - Inherent Benefits can lead to Regulatory Benefits in addition to those specifically provided by Regulatory Flexibility
    - CBER fully engaged in Quality activities

Benefits of Risk Management

- Rigorous and fully developed process development activities and validation studies
- More efficient evaluation of commercial production
  - Identification of risks and corresponding development of mitigation activities to proactively prevent problems.
  - Improved procedures and checklists
  - Fewer deviations/ investigations/ CAPAs
- Effective communication
  - Internal & External
- Recently, risk assessments have been submitted and reviewed by CBER as part of applications

Examples of RA/RM Manufacturing Changes Reviewed by DMPQ/CBER

- Conversion of single product facility to multi-product facility
- Practices to control bioburden
- Cleaning process for transfer piping
- Sterilization/decontamination cycle for live organisms
- Facility operations and process flow to prevent cross contamination
- Changes to container closures

Challenges in Risk Management

- What is the utility of the risk assessment?
  - Will there be useful scientific data to make assessments ?
    - Values assigned for level of risk need to be scientifically sound and justifiable
  - Does this provide false security?
    - "What could go wrong" not fully assessed or not addressed
- What level of detail is needed in the Risk Assessment ?
  - May depend upon several factors
- Recommend contact the review division if you wish to submit a risk assessment

PAT Examples/ Potential Applications

- Cell culture control
- Raw material characterization/ Data Mining
- Control & automation of process flow, buffer preparation in columns centrifuges
- Purification – chromatography – purity (e.g., based upon OD, HPLC, CE, light scattering, spectroscopy, & other analytical methods)
- Mixing/ Blending – using appropriate sensors
- Conjugation - chemical characterization
- Lyophilization - switching between 1st and 2nd stage

- Filled container analysis
  - Content uniformity
  - Moisture, head gas, vacuum, particles
- Rapid Microbial Methods

CBER Approach

- CBER has been participating in development and understanding of QBD, Risk Management, Quality Systems, PAT
- CBER is discussing application of QBD/ Quality initiatives to it products
- Welcome discussions on application of Quality Initiatives

CBER Approach

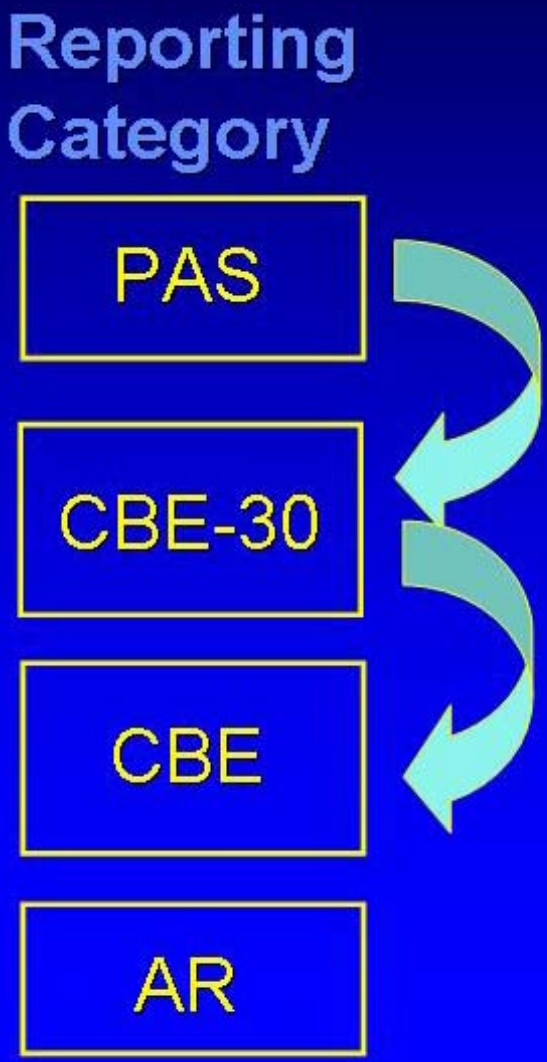
- CBER is well situated to facilitate many QBD/ Quality Initiative activities
  - CBER is involved in understanding, developing and applying new technologies
  - CBER has long history of partnering with manufacturers to develop and implements new technologies
  - Established and experience Integrated Inspection and Review teams and process (e.g., PAT)
  - Science Based - application of science
    - throughout product lifecycle including review and inspection

CBER Approach

- CBER has identified areas of additional preparation
  - CMC/ GMP Risk assessment / risk management training
  - Staff familiarization of newer technologies and approaches
    - Industry/ Vendor presentations
  - Quality System for CMC review

Manage Flexibility for Post Approval Change – Under Discussion

- Existing System provides great flexibility
  - Based upon "Potential" impact of change
- Comparability Protocols (CP) can allow reduction in reporting category
- Information in CP or BLA could serve to allow manufacturer to provide process and product knowledge, risk assessments in addition to existing CP information to justify reducing potential impact of the change
- Consideration for increased broader comparability protocols for some products – those using QBD?
- Make CP more user-friendly
- Internal activities review - assure consistency



New Technologies, New Products, New Challenges

- Applicable to existing and developing products throughout product lifecycle
- Increasing complexity (e.g., complex drugs, drug delivery systems, nanotechnology, biotechnology, drug-device – cellular-tissue combinations, etc.) and anticipated need for patient customization
- **Effective Understanding for Appropriate Regulation**
  - 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
- 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

Role of Science and Critical Path

- **Creating efficient, high quality regulatory pathways where there are none**
- **Applying 21st Century science to improve efficiency and predictability of established regulatory pathways**
- **CBER reviewers and research regulators**
  - expert in biological product evaluation AND standard scientific disciplines..expertise not often seen in standard biomedical discovery research arenas
  - rapidly identify successes, failures, and missed opportunities across whole classes of exciting and innovative products
  - work for the American Public w/o conflicts and play a convening and coordinating role for scientific needs across sponsors
- **FDA staff who are experienced and in product evaluation and scientific disciplines work collaboratively and creatively with sponsors to "get to Yes" & are problem solvers not just problem finders**

Vision for CBER

INNOVATIVE TECHNOLOGY ADVANCING PUBLIC HEALTH

CBER uses sound science and regulatory expertise to:

- **Protect and improve public and individual health in the US and, where feasible, globally**
- **Facilitate development, approval and access to safe and effective products and promising new technologies**
- **Strengthen CBER as a preeminent regulatory organization for biologics**

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