US Perspective on Biological Regulation

PMDA 1st International Symposium on Biologics
Tokyo, Japan
February 15, 2006

Chris Joneckis, Ph.D.

Senior Advisor For CMC Issues
Center For Biologics Evaluation And Research

U.S. Department of Health and Human Services
Food and Drug Administration

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

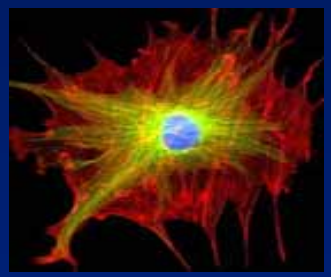
Blood Derivatives

Vaccines

Whole Blood

Somatic Cell & Gene Therapy

Blood Components



Allergenic Extracts

Devices

Xenotransplantation

Tissues

We're Busy

- > 1000 INDs, > 350 sponsor meetings, > 7000 IND/IDE amendments yearly and > 2000 BLA supplements yearly
- Stable high number of BLA and device applications and approvals
- Meeting all drug and device user fee goals
- Moving new technologies forward
- Proactive, collaborative activities for critical public health and preparedness needs
- Dealing with what have become "routine" product emergencies: CT, pandemic, blood, tissue safety and availability

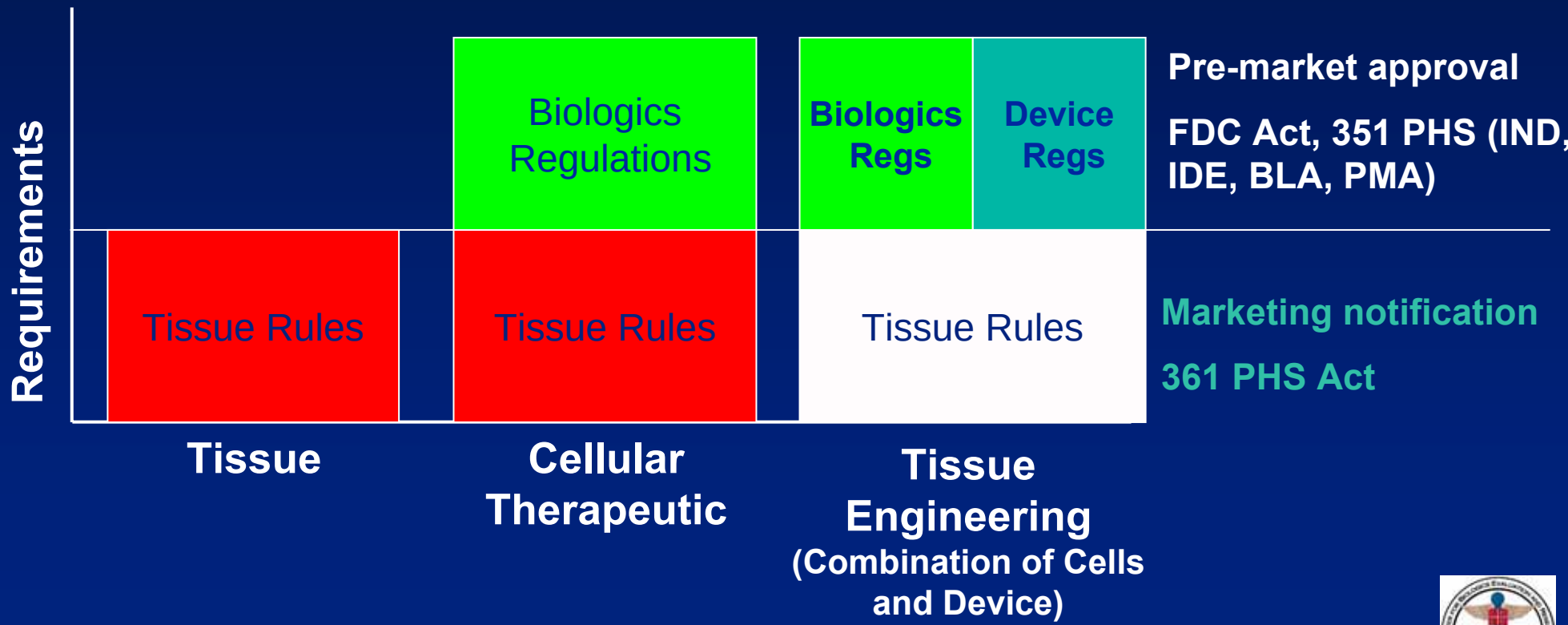
Not Business as Usual

- CBER has adapted to extraordinary circumstances through extraordinary efforts
  - These include proactive measures w/ sister agencies and stakeholders such as:
    - **Meetings to encourage developing new products**
    - **Early and intensive interactions w/ sponsors**
    - **Proactive trips to inspect facilities**
    - **Multiple product development teams**
    - **Expedited review**
    - **Focused, proactive research and standards development in priority areas - assist in more efficient and rapid product development and availability**
  - ***Such approaches successful in preparedness for emerging infectious diseases & medical countermeasures***

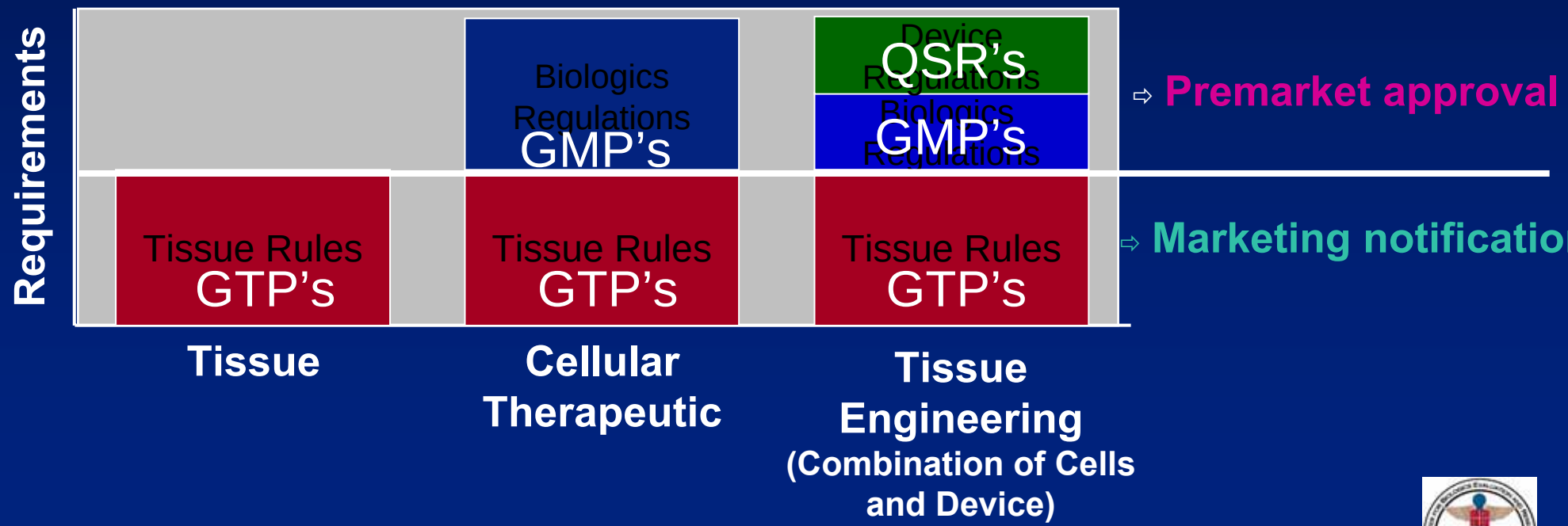
Product Development and Regulation - CBER Philosophy

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

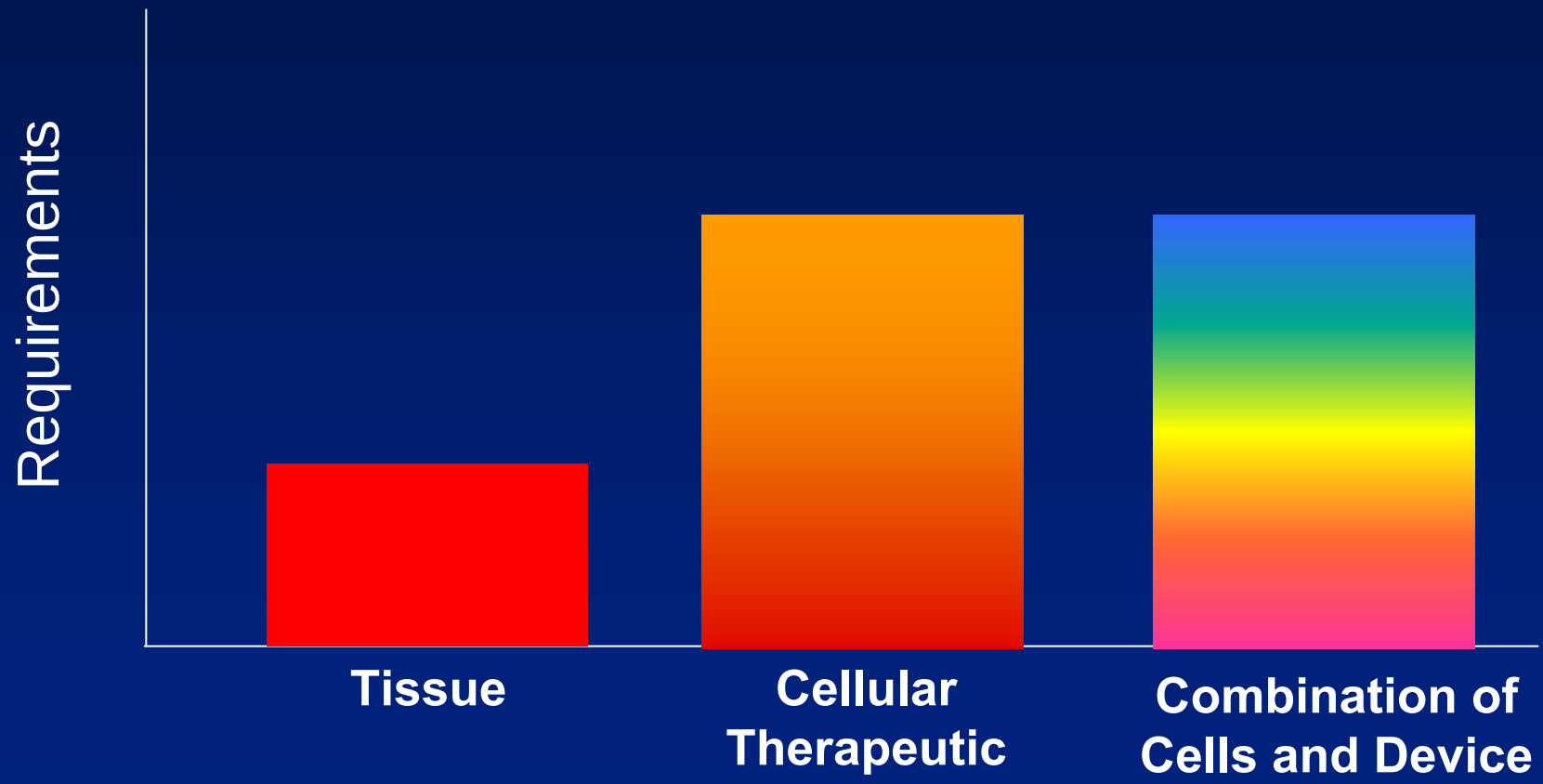
Regulatory Oversight Tissues, Cellular Therapeutics, Tissue Engineering



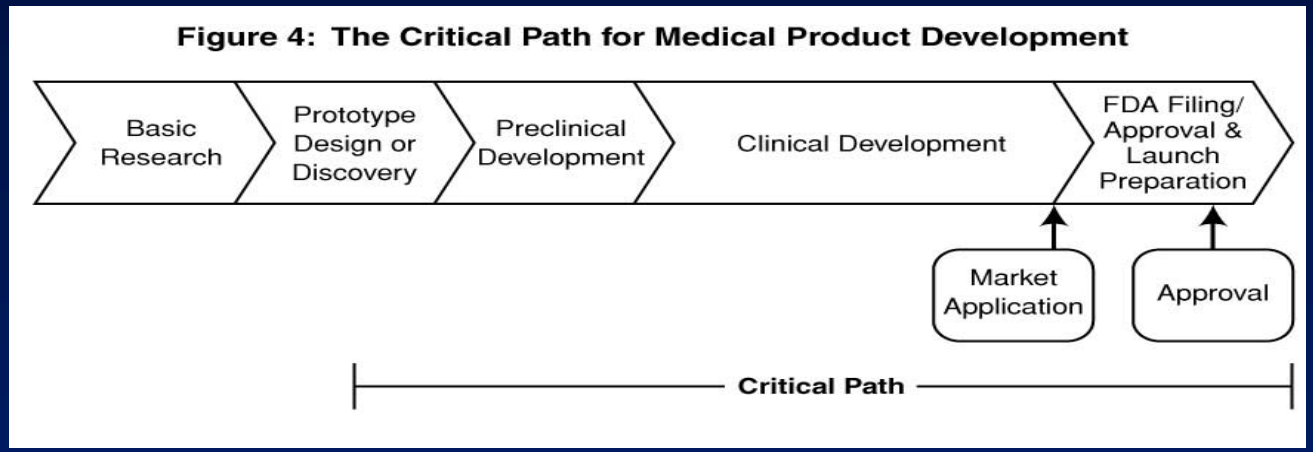
Regulatory Oversight - Tissues, Cellular Therapeutics, Tissue Engineering



In practice, the regulations overlap and are applied in a risk-based fashion



Critical Path



- In these days of increasingly complex medical products and biotechnologies, the FDA needs to be proactive, explicit and transparent to support new safe and effective products moving efficiently through the Critical Path of product evaluation…the path that biological products take on the way from initial discovery to patient use
- In many cases, a regulatory historical path does not exist—Critical Path serves as an explicit science base to inform novel regulatory policy
  - ***Especially high impact and importance where incentives weak – public health, counterterrorism, emerging infectious diseases, blood/tissues, uncertain or niche markets, high risk/novel technologies***
  - ***Preserve a science led FDA***

- ***FDA Critical Path Research Initiative www.fda.gov/oc/initiatives/criticalpath.htm***

CBER Critical Path: Bridge from Discovery to Products for Better Health

Biomedical Discovery

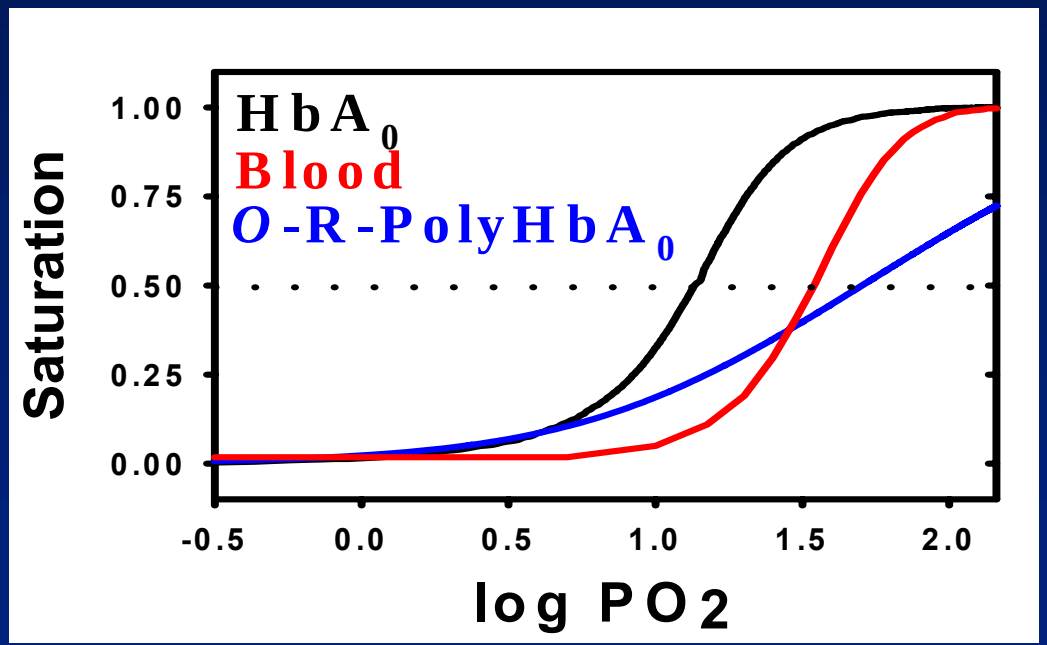
Products Improving Lives and our Nation's Health & Preparedness

- Identify solutions to product challenges: tools & pathways to cross bridge from discovery to products
  - Safety, Medical Utility, Industrialization
- Facilitate product development, safer high quality products, reduce the investment costs for industry

Synthetic Blood Substitutes Hemoglobin-Based Oxygen Carriers (HBOCs)

- HBOC have promising therapeutic benefit but their development is hampered by unexplained toxicity.
- An approach was developed that can serve as a model for a more precise characterization of HBOC structure-function by industry that will help to define and resolve toxicity issues

(A cross-linked and polymerized HBOC)
Hallmarks of Functional Abnormality

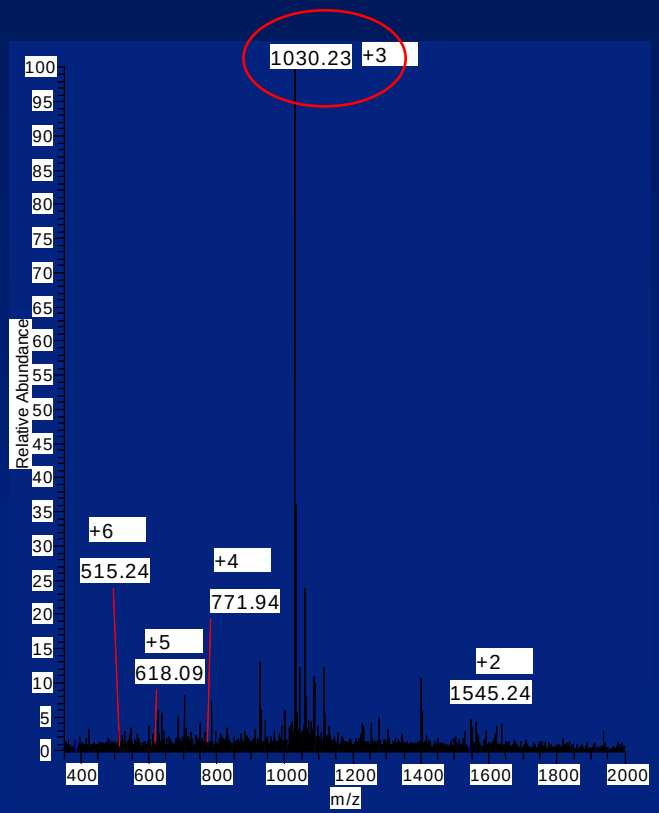


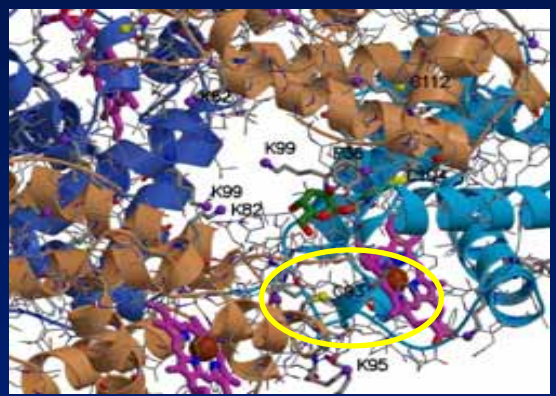
- Non-sigmoidal oxygen equilibrium curve
- Non-saturating
- Non-cooperative (Hill coefficient = 1.0 vs. 2.5)

Biochemistry (2002)

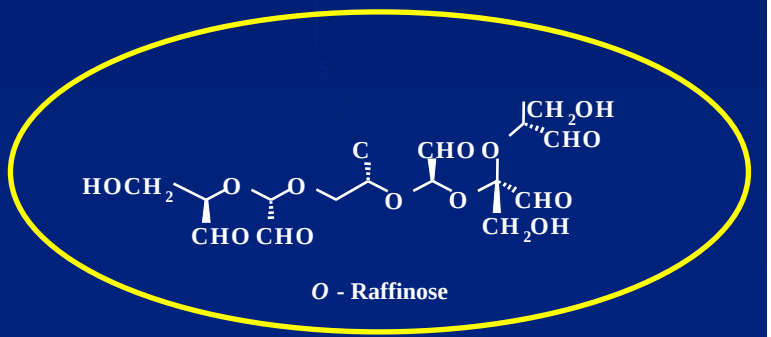
Identification of Chemical Modification Sites on an HBOC by Mass Spectrometry

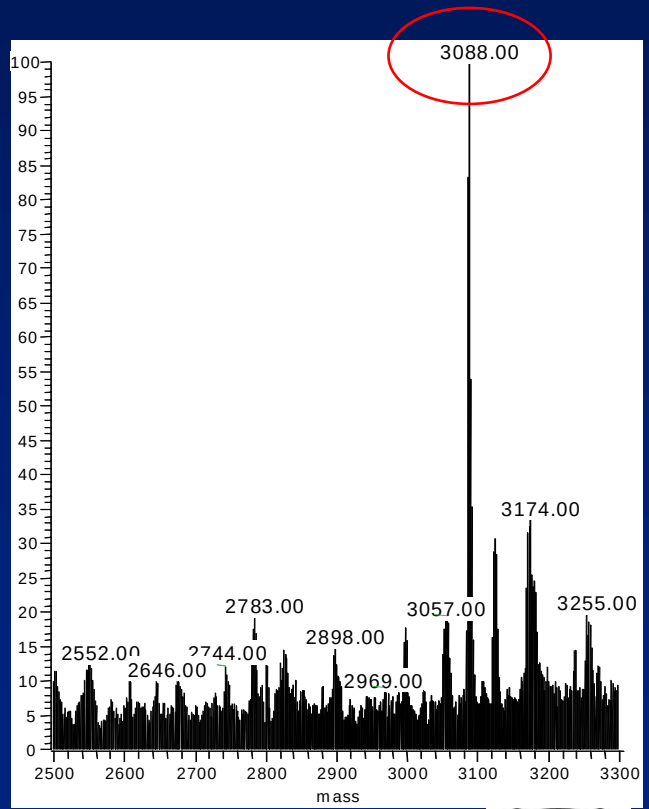
- Unmodified peptide mass = 2064.9 mass units
- Sugar = 483 mass units
- Total mass of *O*-raffinose modified peptide = 3087.9 (2064.9 + 483)





$C_{(\beta 93)}$

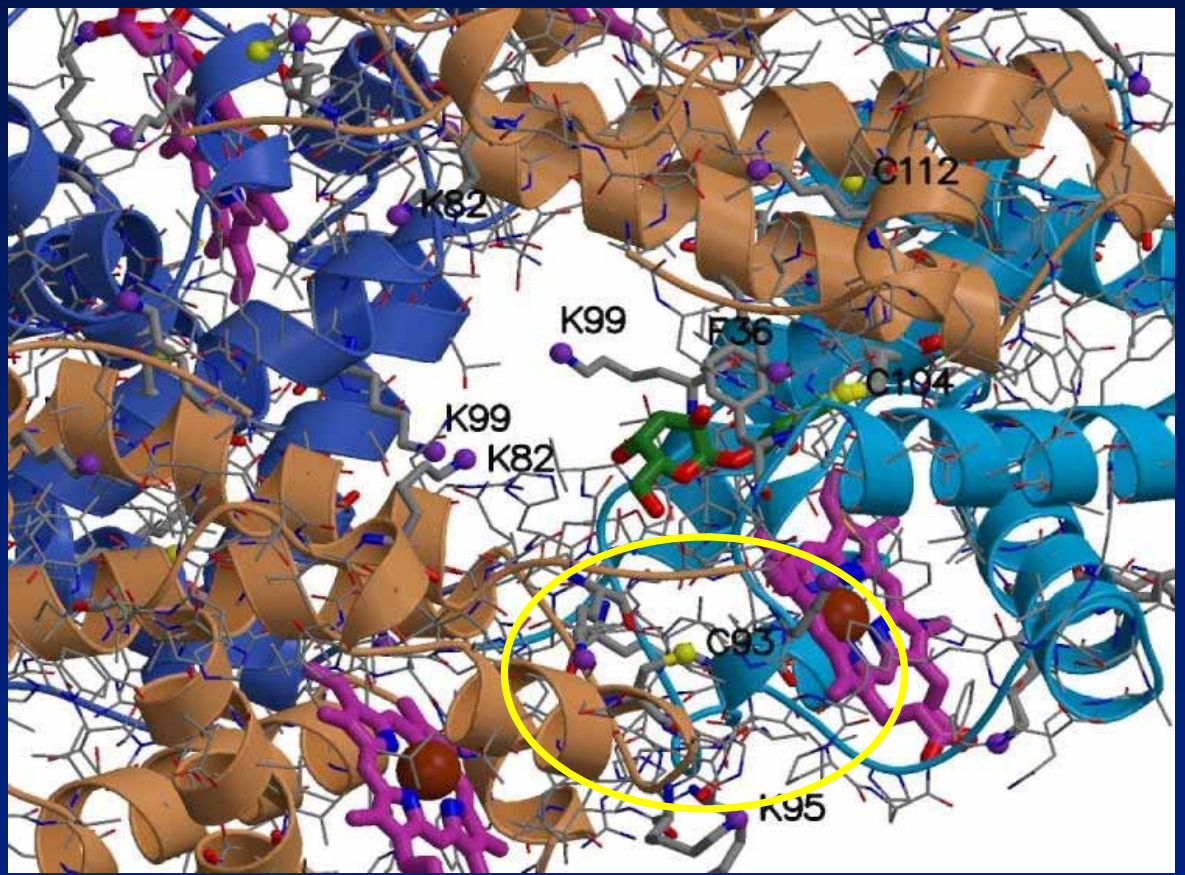




Proteins (2005)

O-R-PolyHbA$_0$: Actual Chemical Modification

(mass spectrometry, light scattering, amino acid analysis and computer simulation)



- Non-specific cross-linking with O-raffinose
- Modified cysteines
- Minimum polymerization

Proteins (2005); in collaboration with the Laboratory of Biophysics, OVRR

General Approaches of FDA Policies to Reduce Risk of Transmitting CJD/ vCJD by Blood Products

- **Reduce risk that donor was exposed to BSE agent**
  - **Dietary exposure & Other exposure: Use of UK bovine insulin**
- **Reduce risk that donor was exposed to vCJD agent of human origin**
  - **Transfusion, UK after 1980**
  - **Transfusion, other BSE country**
- **<u>Problems</u>**
  - **Most deferred donors probably <u>not</u> infected**
  - **Not all potentially infected donors deferred**

Limitation of deferral-based approaches to reduce the risk of blood-borne vCJD

- **Possible solutions**
  - Develop validated reliable screening tests—with confirmatory tests—to detect infected donors and ? re-enter/reassure uninfected donors
  - Develop validated reliable methods to remove (? inactivate or—more likely—separate) infectious TSE agents from products
- **Current status**
  - No FDA-licensed method validated to remove TSE infectivity from red cells, platelets and plasma
  - No FDA-licensed/approved TSE test (for antemortem CJD diagnosis or blood donor screening)
  - Some manufacturers exploring and testing TSA-Agent clearance devices and clearance in plasma derivative products

TSEAC 31 Oct 2005

Validation criteria and possible label claims for devices intended to remove TSE infectivity from blood components

- **TSEAC suggested criteria**
  - ≥ 3 $\log_{10}$ reduction of spiked infectivity (demonstrated by Western blot and bioassay)
  - Remove all detectable infectivity from endogenously infected animal blood
  - ≥ 2 animal models and 2 strains of TSE agent
  - ≥ 1 agent strain derived from cow with BSE or human with vCJD (rodent-adapted)
  - Filtered blood components should maintain functionality at expiry by usual tests

Evaluation of Bovine Derived Materials

- Current Approach - Bovine derived materials
  - Avoidance of bovine derived materials
  - Assure material from BSE-free country “The list” [USDA 9 CFR 94.18]
  - Identify country of origin, tissue source, supplier, stage of manufacture
  - Risk Assessment (e.g., cell banks used to make vaccines)
- Proposed Approach
  - Risk assessment of material – (e.g., tissue source, closed herd)
  - **Use of Materials Derived from Cattle in Medical Products Intended for Use in Humans and Drugs Intended for Use in Ruminants** [Proposed Rule - January 12, 2007]

Meeting Pandemic Flu Challenges: Ongoing Actions

- Increasing manufacturing diversity & capacity
- Developing needed pathways to speed vaccine availability (e.g. guidance's, accelerated approval)
- Facilitating vaccine manufacturing/evaluation/availability
  - current and evolving technologies
  - needed/improved capacity, assays, reagents, virus strains for development, manufacturing and release
  - antigen sparing: adjuvant and delivery
  - "holy grail" vaccines: cross-protective antigens
  - considering priming and prevention strategies
  - assuring vaccine safety and public confidence
- Global assistance, cooperation, harmonization
- Minimize impacts on blood/tissue supplies, safety and availability
- Continuity of operations

Some Issues in Novel Cell Substrates for Production of Vaccines

- Oncogenicity– endogenous viruses, latent viruses, activated oncogenes
- Adventitious agents – unrecognized agent
- Tumorigenicity – degree of tumorigenicity, cell transfer
- Residual DNA – capability to be infectious, oncogenic
- Other mechanisms – (oncogenic proteins, RNA's,)
- Discussions with VRPAC (1998-2005)
  - Discussion of potential risks, available data
  - Discussed in context of specific cell substrates and use
  - Suitable tests and models (e.g., oncogenicity)

Draft Cell Substrate Guidance*

(September 28, 2006)

- Provides guidance to develop comprehensive testing regimens for detection of known and unknown adventitious viruses in novel vaccine cell substrates
- Provides more details of many testing procedures and includes specific tests
- Provides updates of testing procedures
- Includes more detail and scientific rationale for recommendations to allow manufacturer's additional flexibility
- Encourages early discussions between regulators and manufacturers regarding development of specific assays for novel cell substrates
- Evaluations and testing will depend upon several factors (e.g., cell type, history, exposure, manufacturing process) provides examples

*www.fda.gov/cber/gdlns/vaccsubstrates.pdf

Cell Substrates Research

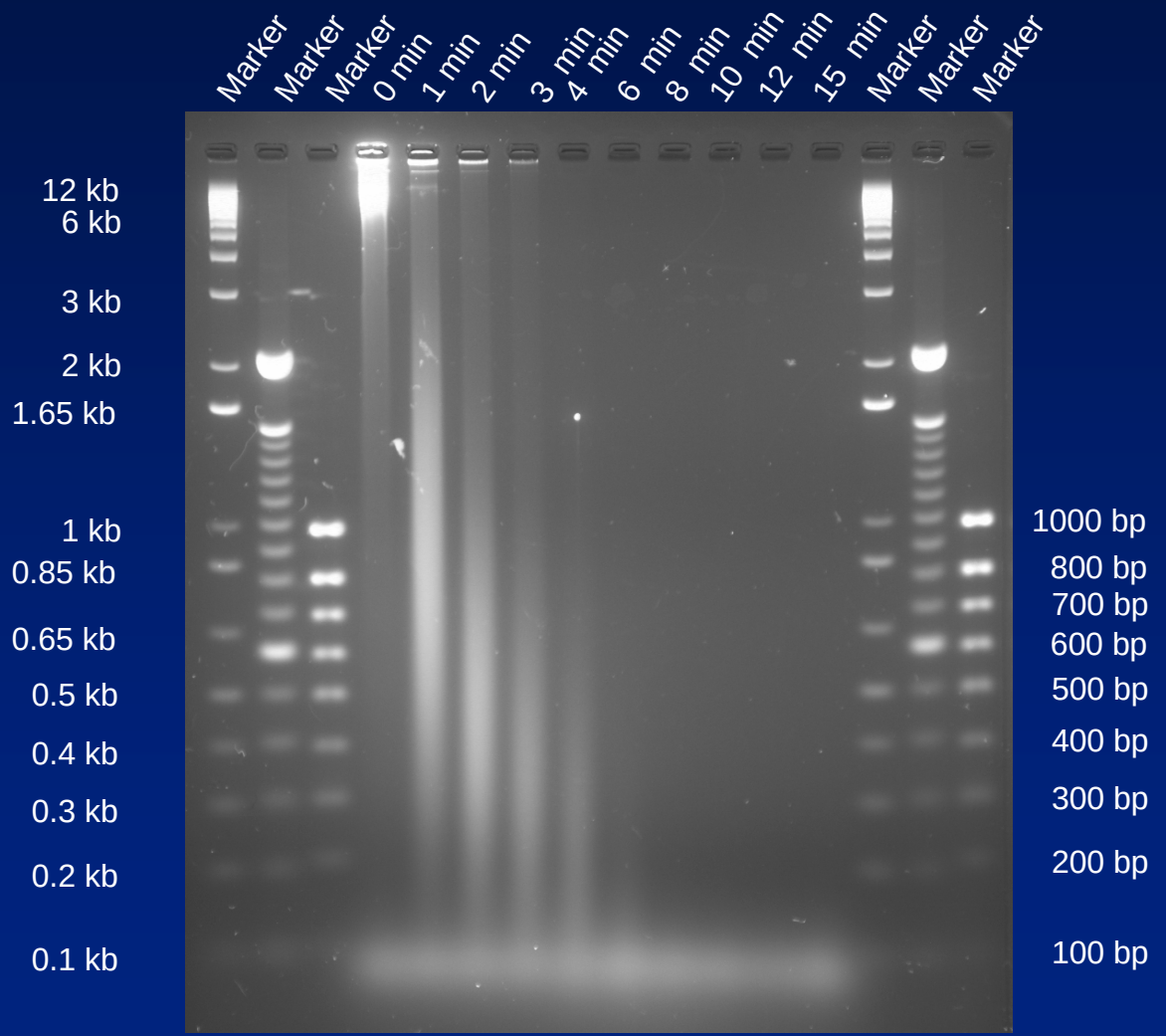
- CBER was funded to develop tools for evaluating cell substrates used to manufacture biological products.
  - Assessing the in vivo oncogenicity of cellular DNA
  - Animal and cell-based models for identifying latent/ occult viral contamination
  - PCR-based and other novel approaches for identifying infectious contaminants
  - TSE contamination of cell substrates
  - Microarray-based methods for mycoplasma detection
- These activities should provide additional understanding to assess risk used in managing regulatory decisions and
- Provide models/ tests/ algorithm for testing of cell substrates

- **Evaluation of novel cell substrates is evolving and recommendations may be revised**

Rationale for Assessing DNA Infectivity

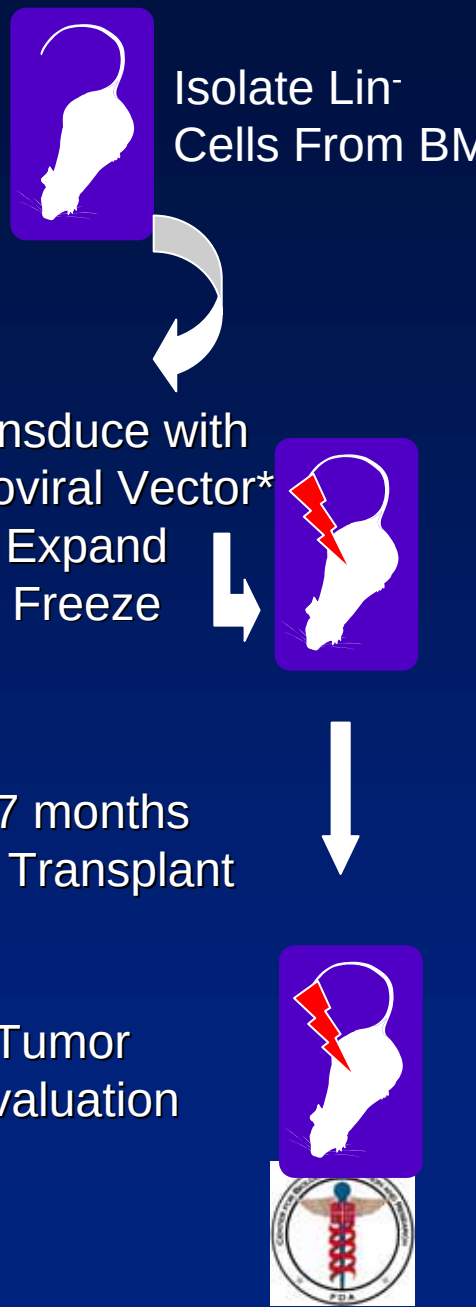
- Infectivity risk may be higher than DNA oncogenicity risk (VRPAC, 1999)
- DNA infectivity has been incompletely studied
- Clearance of DNA infectivity will also clear DNA oncogenicity
- Assay will allow other aspects of DNA activity to be studied

Elimination of HIV DNA Infectivity With Benzonase



Improving the Safety of Retroviral Vectors

- Success of retroviral vectors may be limited by potential for vector-mediated insert ional tumorigenesis
- CBER Collaboration with NIH/ NIEHS - Design and test a preclinical mouse model for assessing preclinical risk of cancer adverse events from retroviral vector-mediated insert ional tumorigenesis.
- Selected mouse model mimic clinical situation
  - Bone marrow transplantation
  - Integration into oncogene
- Assess the effect of vector modifications on reducing the risk of cancer adverse events
  - vector dose,
  - deleting the viral enhancer
  - using an insulator element
  - Other vectors?
- **Goal: Preserve the therapeutic benefit and decrease avoidable risks – reduce cancer risk**



Problem Solving Research

- FDA/ CBER focus is unique: research managed to identify solutions to product development challenges
- Driven by FDA perspectives & data – the “Big Picture“
- Performed by active researcher-reviewers on multidisciplinary teams
- Reviewers help identify issues & set research priorities
- Not NIH research - applied to concrete product issues
- Not industry research - applied to product issues
- Often cross - cutting – clinical, product, statistical elements
- Collaborative & Leveraging: internal and external resources

Collaboration - Some Examples

- **Inter Center, InterAgency, Intergovernmental**
- **Training - Interagency Oncology Task Force (IOTF) (http://iotftraining.nci.nih.gov)**
  - FDA & NCI train NCI Fellows in Regulatory practices and research aimed at facilitating product evaluation and development
- **Training - Collaborative Scientific Training Program (www.fda.gov/cber/cstp/cstp.htm)**
  - Facilitate research and training partnerships that engage scientific partners in pursuing the goals of the Critical Path Initiative
  - Projects or activities can be tailored to address the specific scientific needs and goals of CBER and the Collaborator Institution
    - ORGANISATIONS –academic institutions, international regulatory agencies, non-profits, US government agencies
    - PROJECTS ACTIVITIES -scientific research/ training, meetings workshops, piloting new methods & standards
    - PARTICIPATING STAFF – scientist, clinicians, fellows, postdocs, interns

Global Harmonization and Collaboration: Examples

- FDA/WHO/Health Canada Pandemic Regulators
- WHO and WHO Collaborating Center
  - Expert Committee on Biologic Standards, SAGE, GCVS
  - Influenza, vaccines xeno and gene therapy
- Blood:
  - GCBS, WHO "Circle of Regulators" – safety screening standards – hosting global meeting
- ICH (including GT) , PIC-S, ICDRA
- Information sharing & encouraging global product development plans/coordinated regulation
  - FDA has agreements with many countries to exchange information of regulatory value

Standards

- CBER product testing, research labs, clinical and product expert reviewers, IT staff all participate – critical in blood and vaccine safety, supply
- Growing interest in outside standards setting organizations & activities - frequently global
- **In FY 2006,**
  - 86 CBER staff participated in
  - 76 standards activities
  - with 28 organizations
  - All portfolio areas, Blood, Vaccines, C&GT, IT, Clinical, PV
- Organizations include:
  - Accredited voluntary consensus standards organizations (e.g., ASTM, ISO, HL-7)
  - Industry, Trade Groups (e.g., ISCT, AABB, AATB)
  - International (e.g., ICH, GHTF, WHO/ECBS, PAHO, NIBSC, PEI, TGA)

Recent Standards Activities Some Examples

- Blood:
  - Coagulation and other proteins (many collaborative with WHO, NIBSC, others):
    - Factor VIII, thrombin, **α1-PI**, IGIV and HBIG (anti-measles, polio, HBs), prekallikrein activator, anti-D, anti-A and anti-B hemagglutinins (w/ NIBSC, EDQM)
  - Nucleic acid: HIV, HIV-2, HAV, HBV, HCV, parvovirus B19
  - Multiple panels, including HIV, HIV for uncommon subtypes, HTLV, Chagas
  - Discussion with Industry Trade Associations
    - Blood and Blood Components Container Labeling (AABB)

Recent Standards Activities
Some Examples

- Cell and Gene Therapy:
  - Adenovirus, retrovirus, AAV (ongoing), flow cytometry, external RNA for microarray and PCR assays
  - Discussion w VCS and industry trade associations
- Vaccines:
  - flu strains, reagents, transgenic mouse polio neurovirulence, rat mumps neurovirulence (ongoing with WHO, NIBSC collaborated)
- IT:
  - CBER lead in approval at HL-7 of the Individual Case Safety Report standard

Challenges with Standards

- **Formalizing participation across Agency and Center**
  - Participants represent CBER & FDA view
  - Participation does not constitute endorsement in standard
- **Challenges with Standards**
  - When to develop a guidance or standard?
  - External or internal development?
  - What group(s) to participate? How to participate?
  - How to recognize a standard?
  - Determining acceptability of standard for a specific application (e.g., product)
  - Greater International Discussion/ Collaborations
  - Utility For Biologics?

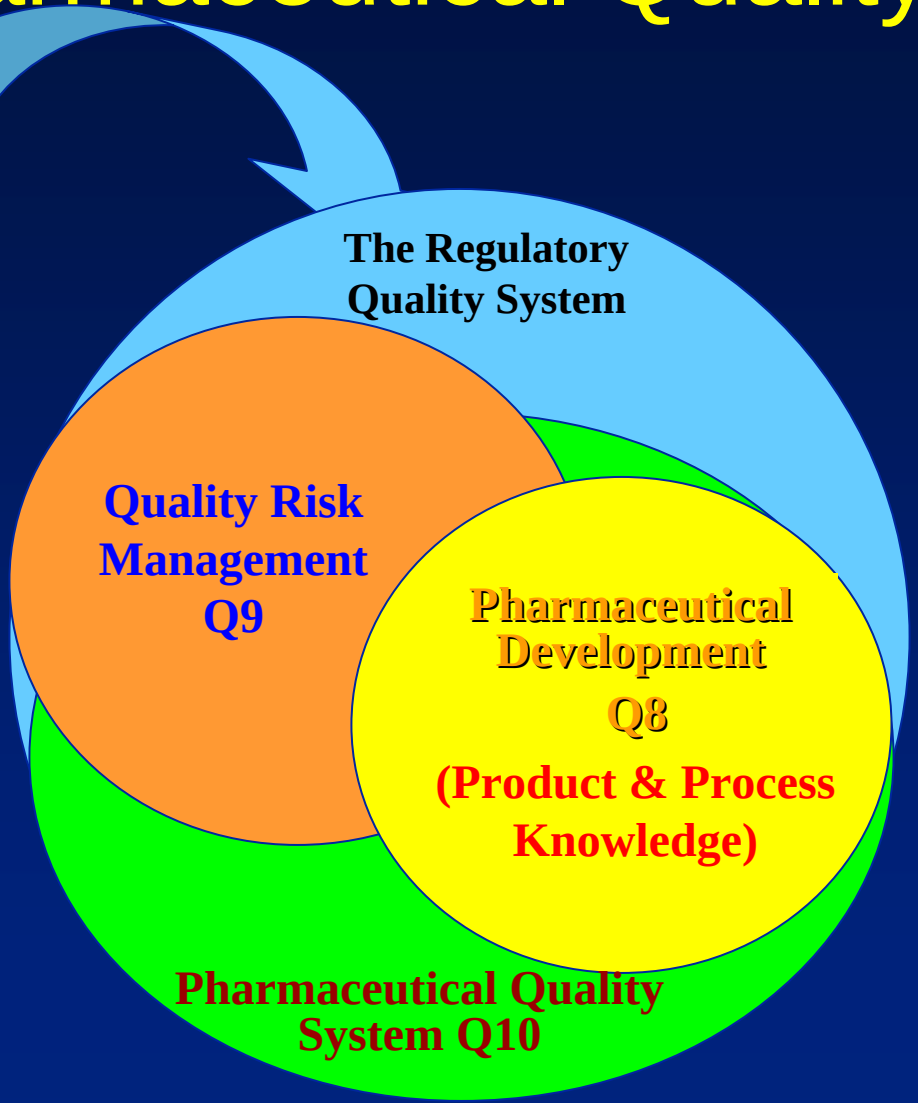
Manufacturing and Quality

- Enhance scientific tools and assessment for manufacturing
  - Quality By Design, Risk Management and Quality Systems (Q8, Q9, Q10)
  - Multiple Approach to Process Understanding and Process Control
- Manufacturing Site Visits
- Risk-based compliance programs
  - Evaluate existing programs
  - Expand to new areas

The Proposed Pharmaceutical Quality System

ICH / non-ICH topics

Includes



"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*

Implementation Benefits of Effective Q8, Q9 & Quality System

- Assure appropriate CQA and variables are developed and assessed
- Assure appropriate controls are designed and carried forward
- Validation studies developed (modern concept of validation)
- Assure development knowledge and risk information is transferred and used appropriately
  - Ideally, correctly predict impact of change and maintain (improve) product quality
- Better process control and monitoring
  - Improved process capability

Implementation Benefits of Effective Q8, Q9 and Quality System

- Inherent Benefits can lead to Regulatory Benefits
  - Greater Efficiency in Review & Inspection
  - Better Regulatory Compliance
- Additional Potential Regulatory Flexibility
  - Impact on
    - CMC Review
    - Change control and continual improvement
    - Submission of post approval changes
    - Inspection
    - Other potential regulatory benefits?
- Win:Win:Win – Patient, Industry, Regulator

Reporting Manufacturing Changes (Current System)21 CFR 601.12, July 24, 1997)

- Changes to an approved application
  - » product, production process, quality control, equipment, testing, facilities, labeling
- Evaluate the change(s) for potential to impact the DS & DP product quality with regard to safety *and efficacy*
- Comparability Study – analytical, preclinical, clinical,
- Potential for change to have an adverse effect on a products identity, strength, quality, purity, or potency as they may relate to its safety or effectiveness.
- Potential determines reporting categories
- Suggested changes by reporting categories in Guidance

Reporting Manufacturing (Post Approval) Changes

Reporting Category	Potential For Adverse Impact	Product Distribution
PAS	Substantial	upon receipt of FDA approval
CBE-30	Moderate	30 days from FDA receipt
CBE	Moderate	upon FDA receipt
AR	Minimal	upon study completion

Reporting Manufacturing Changes: Current Risk Based Approach

Reporting Category	Potential For Adverse Impact	Product Distribution
PAS	Substantial	upon receipt of FDA approval
CBE-30	Moderate	30 days from FDA receipt
CBE	Moderate	upon FDA receipt
AR	Minimal	upon study completion

Comparability Protocol

Reporting Manufacturing Changes

- Current activities
  - Revising “Changes to Be Reported Guidance for Biologics”
    - Revaluate type of changes for biologics in each reporting category based upon experience and risk
- How can impact of change can be better assured? How can risk be reduced?
  - **Considerations**
    - Encourage use of Comparability Protocol
      - Consideration for additional flexibility in use
    - Demonstration of knowledge and process control
    - Better evaluation and communication of impact/ risk – optional risk assessments may be beneficial
    - Effective Quality Systems at manufacturer

Risked-based Regulatory Oversight (Some factors)

- Type of Product
  - complexity, ability to be characterized
  - development of meaningful quality attributes
  - mechanism of action
  - established relationship to safety and efficacy
  - ability to predict outcome of manufacturing change
- Intended use
- Manufacturing complexity & control
- Manufacturing operations critical to safety of the product
- Products that serve a critical medical need, critical public health impact
- Compliance history, compliance status

Thank you

- We are in the midst of new advances in targeted therapy, novel products, vaccines and other areas of medical research leading to development of safe and effective new medicines for the 21st century.
- New technologies need expert, innovative & interactive science, new models, standards and assays.
- We see a positive future with exciting science and great opportunity for everyone.

www.fda.gov/cber/