Opportunities for Harmonization Through Standards and Convergence

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IPFA/BCA The Future for Blood and Plasma Donations

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Disclaimer

My comments are an informal communication and represent my own best judgment. These comments do not bind or obligate FDA.

Topics

- Factors driving international regulatory harmonization of blood products
- Challenges to harmonization
- Opportunities for convergence
  - Standards development
  - Regulatory and non regulatory collaborations
- Conclusions

Factors Driving Regulatory Harmonization of Blood Products

- Global goal (including of regulators and industry) to improve blood product safety, supply, and global health
  - EID's are a global danger. Shared approach can lead to control or elimination of threat
- Streamlining global product development help products to reach more patients sooner

Advantages of Harmonization

- Applying the best scientific and regulatory judgment to our decision-making
- Leveraging resources
- Economic factors
  - High demand for plasma derivatives have created unmet international needs for plasma
  - Industry players include large multinationals
  - In US, as need for RBC declines, plasma is a source of revenue for blood collection centers

Universal Agreement

- Protect donors of blood and blood components by requiring establishments to evaluate donors for factors that may cause donation to adversely affect their health
- Assure the safety, purity, and potency of the blood and blood component products used for transfusion and for further manufacture

Challenges to Harmonization

- National interests may not align
  - Goals of self-sufficiency
  - Desire to nurture national industries
  - Different pathways to product approval have merit
- Differences in population norms. What is normal?
- Epidemiological differences matter
  - e.g. malaria, Chagas' Disease, vCJD, HTLV
- Diverse social and economic conditions can affect blood policy
  - Safety and acceptability of paid donors
  - Cost:benefit for leukocyte reduction and NAT

Challenges to Harmonization

- Harmonize with whom, e.g, EDQM, WHO?
- Is there a unified industry position internationally?

How strong are the factors in favor of harmonization versus those opposing?

- "If it ain't broke, don't fix it"
- Change of standards costs money
- Does the scientific evidence support a need for change?
- Compelling safety issues?
- Regulatory constraints: difficulty in changing regulations

Examples of Non-uniform Standards

	US CFR , guidance	EDQM Guide	PhEur
Hemoglobin, men	12.5 g/dl	13.5 g/dl	
Cryoppt, FVIII/ unit	≥ 80	≥ 70	
Cryoppt, fibrinogen/unit	≥150mg	≥140mg	
Plasma freezing conditions	≤-20 °C (Source Plasma) ≤-18 °C (FFP)		Frozen to a core temp of ≤-25°C in ≤12 hr (labile products)
Time from collection to freezing	place in freezer immediately (2 hr) (Source Plasma)		≤24 hrs (labile products)

Local Harmonization

- Blood or plasma collection facility can adapt to foreign regulatory requirements while meeting US minimum requirements
- Example: SOPs of some Source Plasma collectors specify freezing and storage conditions that meet PhEur requirements

Opportunities for Public Dialogue

Exchange of Information

Public

- Meetings of professional societies, trade organizations, e.g., ISTH, ASH, AABB, ATHN, IPFA, IPPC, ICDRA, ISBT, SoGAT, PPTA Plasma Forum
- Ad hoc and annual meetings w patient group, e.g., WFH, NHF, IDF
- Workshops
- FDA sponsored Patient Focus Meetings
- Advisory, e.g., BPAC, ACBTS; emphasis on transparency

Exchange of Information

Industry requested (narrow focus)

- US trade group-hosted meeting, e.g., AABB, ABC, PPTA, invite FDA to discuss narrow range of issues
- Non regulatory meetings with individual sponsors
  - focused, brief meetings (telecon or internet preferred)
  - future plans that may affect FDA's inspectional and regulatory agendas, e.g., opening of new collection center

Rule Making and Guidances

- Public input into the rule making process, including submitting proposals, and in the development of Guidance documents.
- **Data driven**
- Proposals are published in the Federal Register and go through a period of notice and comment
- https://www.federalregister.gov/uploads/2011/01/the_rulemaking_process.pdf
- Example:
  - Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use; Final Rule, May 2015
- **Rationale for decisions are provided**

Opportunities for Harmonization through Standards Development

Standards Development Opportunities

- World Health Organization
  - Expert Committee on Biological Standardization (ECBS)
  - Collaborating Center for Biological Standardization
- International Conference on Harmonization (ICH)
- Pharmaceutical Inspection Co-operation Scheme and Pharmaceutical Inspection Convention (PIC/S)
- Council of Europe: Guide to the Preparation, Use and Quality Assurance of Blood Components

Standards Work in OBRR

Written standards (National and International)

AABB	conditions for the collection and processing of blood
AAMI	standards for blood filters
ASTM	cytotoxicity of nanofilters
CLSI	laboratory testing and diagnosis of HIV
EDQM	European Committee on Blood Transfusion, Blood Guide
ICH	MedDRA management board
ISO	health informatics
USP	chapter development, e.g., aggregates in therapeutic protein
WHO	Expert Committee on Biological Standards

Physical Standards

WHO-NIBSC	International potency reference standards, e.g. clotting factors
WHO	Reference panels, e.g., HBV genotype DNA NAT panel, Dengue serotypes

Opportunities for Harmonization through Regulatory Convergence

Joint Regulatory Advice to Sponsors

- EMA-FDA Parallel Scientific Advice:
  - FDA and EMA confer in structured process, at sponsor request, in development phase of product
    - Exchange of views on scientific questions posed by sponsor, with goal (but not requirement) of aligned regulatory positions
    - Increasing dialogue between the two agencies and sponsors
      - Optimizes product development
      - Avoids unnecessary testing replication or diverse testing methodologies

EMA-HC-FDA Blood "Cluster" Meetings

- "Cluster" denotes more intensive, routine exchange of information/discussion of issues
- EMA, HC, and FDA confidentiality arrangement: can share confidential information (excludes trade secret, patient identification)
- Meets periodically depending on issues

Types of Topics:

- Issues specific to a product or class of product (safety, quality, efficacy)
- Policy exchanges

EMA-FDA Blood Cluster: Adverse Event Discussion

- Who? What product?
  - Share information about manufacturer, product lots
- Where? When?
  - Occurrence of AEs
  - Manufacturing sites: relation to product defect
- How?
  - Root cause analysis
  - Assay to detect cause?
- Do other manufacturers have similar problems?
- Follow up
  - Workshop
  - Monograph changes
  - Surveillance
  - Regulatory activity may differ depending on independent assessment by regulatory authorities and regional regulatory requirements

EDQM Expert Group 6B

- 6B develops PhEur standards re blood products; PhEur has legal standing in member states.
- FDA has Observer status, non voting
- Exchange information
- Gain insight into rationale for decisions
- Potential for working cooperatively to establish common assay conditions for potency measurements, and conditions for plasma preparation, among other projects

Regulatory Convergence in Crisis Example: Ebola

- WHO's Blood Regulatory Network (BRN) involved: US, Germany, Canada, France, Japan, Switzerland, Australia
- Confidentiality Arrangement between FDA and WHO: share non-public information to address potential public health emergency of international concern.
- Frequent communications to exchange information and share updates regarding Ebola focused activities
- Collaboration to find convergence on regulatory pathways for clinical development of Ebola vaccines and blood collection policies

Potential New Opportunities for Engagement?

- **ICH**
  - Changes to ICH membership and governance
  - Focus global pharmaceutical regulatory harmonization work in one venue
  - More active involvement of regulatory authorities and industry stakeholders in pharmaceutical harmonization work
  - Increase the involvement of global industry sectors that are affected by ICH guidelines
- **Mutual Reliance Initiative (MRI)**
  - FDA-EU to evaluate our comparable regulatory frameworks for inspections of manufacturers of human pharmaceuticals to determine if we can rely on each other's inspectional information. Transatlantic Trade and Investment Partnership (TTIP) in process.

Conclusions

- Powerful forces favor global harmonization
  - Global desire to enhance product quality, patient safety and public health
  - Economic and political factors
- Explicit formal mechanisms to achieve regulatory harmonization for blood and plasma do not exist at present
- However, mechanisms that foster regulatory convergence are proliferating and are gaining influence, particularly in the areas of standardization and fora for regulatory dialogue