How Should Regulators Assess and Manage Risks of Blood Products?

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How Should Regulators Assess and Manage Risks of Blood Products?

• The need for and role of the blood regulator
• Defining the controversy over risk based decision making for blood safety
• Risk management frameworks for blood safety
  – WHO Aide- Mémoire on Good Policy Process for Blood Safety and Availability
  – Canadian Consensus Conference on Risk Based Decision Making for Blood Safety
• FDA’s approach to EID agents
  – Basic questions
  – Issues regarding DENV, CHKV and Babesia
  – Use of quantitative risk assessments
• Summary
The Need for Blood Regulation -I

- Blood transfusion is an essential therapy that saves lives in acute emergencies, improves quality of life in numerous conditions and enables many complex medical and surgical procedures.
- Plasma products likewise contribute in major ways to life and health.
- However, the inherent risks of blood and the complexity of providing adequate, timely and equitable access to safe blood products require an organized national or regional blood system.
- Within that system, a competent blood regulatory authority assures that appropriate standards are met for production of blood products and monitoring of blood safety.
The Need for Blood Regulation - II

• In 1975, the World Health Assembly, WHO passed resolution WHA 28.72 which first established globally the principle of nationally supported, managed and coordinated blood systems
  – Many subsequent resolutions have been directed at strengthening blood systems

• In 2010, WHA resolution 63.12 recognized that “stringent regulatory control is vital in assuring the quality and safety of blood products…” and urged Member States to “update their national regulations … in order to ensure that regulatory control in the area of quality and safety of blood products across the entire transfusion chain meets internationally recognized standards.”
Role of the Blood Regulator

• Assuring the quality, safety and availability of blood and blood products is a public health responsibility

• Blood regulators function as a public trust playing a fundamental role as “gate keepers” and “overseers” in determining the strategies, technologies and resources directed at assuring equitable availability of blood products that meet quality standards for safety, efficacy and consistency

• Decisions of blood regulators have important economic and public health consequences, however, multiple organizations collectively “own” blood safety risks and their controls as part of a complex network
Defining the Controversy - I

• In the wake of the AIDS tragedy, and related actual or perceived institutional failures, the risks of blood therapies have become a major public concern
  – Threats from hepatitis viruses and from newly emerging diseases including vCJD and West Nile virus have intensified these concerns
• In response, over the last three decades, blood regulators have tended more aggressively to adopt safety measures that minimize risk, however,
  – A goal of zero risk is not compatible with available resources
  – Absent a structured process, decisions made in the face of uncertainties can be inconsistent
  – The same interventions may not be appropriate in all jurisdictions
Defining the Controversy - II

• Implementation of blood safety measures inherently involves trade-offs between the achievable levels of safety, product availability, and costs

• Evaluation of risks is both scientific and social

• Blood regulators must consider:
  – Scientific knowledge and uncertainty regarding product risks
  – Feasibility and impact of safety measures
  – Societal perceptions and expectations

• A “Good Policy Process” including a defined framework is needed to optimize the effectiveness, efficiency and acceptability of regulatory decisions on blood safety
Defining the Controversy - III

• Escalating unit costs of blood safety measures and the lack of integration with overall risk and resource management have prompted efforts to establish internationally recognized decision making principles.

• Efforts to enhance the quality of decision making for blood safety and availability have focused in at least two major areas:
  – Development of a standardized decision making process that incorporates widely adopted principles and including application of the “Precautionary Principle” as a basis for action in the face of uncertainty.
  – Wider adoption of formal decision making tools by regulators, including use of quantitative risk assessment methodologies.
Two recent initiatives have helped to define a standardized framework for blood safety decision making:

  
  www.who.int/entity/bloodsafety/publications/who_eht_08_02/en

- In October 2010, Canadian Blood Services hosted an International Consensus Conference to explore the feasibility of a standardized risk-based decision-making process for blood safety based on an in-depth understanding of the limitations.

WHO Aide-Mémoire on Good Policy Process: Principles

- Decisions based on scientific, medical and epidemiological evidence
- Consideration of economic, ethical and social dimensions
- Efficacy and cost-effectiveness
- Partnership and active participation by relevant stakeholders
- Transparency
- Effective Communication
Aide-Mémoire on Good Policy Process: Assessing Policies

• Impact on health outcomes
• Access and fairness of policies
• Cost and value for money
• Scientific evidence to back policy
• Operational capacity of institutions involved
• Legal issues and international agreements
• Risks, public health and safety
Aide-Mémoire on Good Policy Process: Structured Policy-Making Process

- Situation analysis, definition of problem and risk identification
- Identification of policy alternatives
- Risk assessment and analysis
- Identification of preferred policy option and policy formulation
- Policy implementation
- Monitoring and evaluation
- Risk management
Canadian Consensus Conference on Risk-Based Decision Making for Blood Safety

Following a set of expert presentations, a panel of experts in risk management, communication and health policy, plus lay and patient representatives was asked the following questions:

1. What are the key aspects and limitations of current decision making in blood safety?
2. What are the best practices in decision making to be leveraged and in what manner should they be applied?
3. What benefits can be achieved in the development of a framework?
4. What are the components to be incorporated in the design of a framework and what does the framework look like?
5. What are the necessary next steps to agree upon and implement a risk-based decision making framework for blood organizations?
Findings of the Canadian Consensus Panel - I

• The current regulatory focus on minimizing product risk with only limited consideration of costs is not sustainable
• Absent an integrated risk management framework, the current condition of uncertainty, suspicion and at times poor decisions will persist
• Reliance solely on regulatory oversight is important, but limiting
• Progress towards a new decision making framework will require significant commitments and investments including in biovigilance/hemovigilance, research, innovation, education, staff training and infrastructure
Findings of the Canadian Consensus Panel - II

• Risks are borne exclusively by the recipients of blood (i.e., the risks and benefits are not equally distributed to different parties)
  – As a consequence, standard risk-based decision making frameworks will not be immediately or directly transferable to the issue of blood

• Components of an integrated risk management framework are well-known
  – The challenge comes in operationalizing these components in the context of the “vein-to-vein” blood system
Recommendations of the Canadian Consensus Panel: Five Key Points

• An integrated risk management framework that encompasses “vein to vein,” and beyond
• Decision making based on transparent principles of risk management
• A system that balances risks, costs and benefits in a sustainable manner
• Meaningful engagement with interested and affected parties throughout the process of risk decision making
• Adherence to well-established ethical principles to ensure that the rights of both donors and patients are respected
Addressing Uncertainty of Risk

• While risk assessment, risk management and risk communication are fundamental to decision making for blood safety and availability, a dilemma that regulators often face is how to address uncertainty.

• A variably formulated concept described as the “precautionary principle” dictates that in times of uncertainty regulators should take actions to reduce a perceived risk despite the inadequacy of the available scientific data.

  – Some countries have legally adopted a precautionary principle applicable to blood safety decision making.

  – Considerations for application of the “precautionary principle” are discussed in a communication from the European Commission (Brussels, 2.2.2000, COM (2000) 1 final)
Precautionary measures should be considered within the context of a structured analysis of risk. When applied, the measures should be:

- Proportionate to the chosen level of protection
- Non-discriminatory in their application
- Consistent with similar measures already taken
- Based on an examination of the potential benefits and costs (including where appropriate and feasible an economic cost/benefit analysis)
- Subject to review in the light of new scientific data, and
- Capable of assigning responsibility for producing the scientific evidence necessary for a more comprehensive risk assessment
FDA’s Approach to EID Agents: Basic Questions - I

- Is the agent blood borne and/or viable in tissues?
- Does the agent survive product processing and storage?
- Is there a significant prevalence in donors?
- Can the agent be transmitted by transfusion or transplantation?
- Is there an asymptomatic period of infectivity?
- What is the disease attack rate and clinical impact on recipients?
FDA’s Approach to EID Agents: Basic Questions - II

• Can we screen donors for risk factors?
• Can we test donors for evidence of the infection?
• Are the available tests sufficiently sensitive to provide a meaningful safety benefit?
• Are the available tests sufficiently specific to avoid compromising product availability?
• Can the system bear the burdens of screening and testing?
• Are there suitable alternative strategies?
Dengue Virus (DENV) is the Most Common Vector-borne Virus

- Threatens 2.5 billion people worldwide
- More than 50 million infections occur each year
- More than 24,000 deaths per year
- Can be transfusion transmitted
Autochthonous DENV in the U.S.

Potential safety interventions need to address both endemic and non-endemic areas of the US.
Chikungunya Outbreaks in the Indian Ocean Region 2004-2006*

Mosquito Vectors for Dengue and Chikungunya Viruses Exist in the US

Aedes aegypti  Aedes albopictus

What steps should be taken now to prepare for a potential US outbreak of Chikungunya virus?
Transfusion-transmitted Babesiosis Cases in the US 2004-2008 by State of Donation

For two cases, state of donation is unknown

N=63*

Should regional testing be implemented? If so, with what tests and in which states? Should this be year-round?
FDA’s Use of Quantitative Risk Assessments in Blood Safety Decisions

• vCJD
  – Donor deferral strategy
  – Risk management of clotting Factors (FVIII, FIX, FXI)
  – Risk communication for blood components
• Malaria risk in Mexico
  – Consideration to accept risk in low endemic states
• Donor testing for Chagas Disease
  – Consideration of one time testing
• Safety strategy for babesiosis
  – Consideration of a regional testing policy
• Reexamination of indefinite deferral for MSM
Quantitative Risk Assessment for EIDs

• General Approach
  – Hazard identification
  – Dose-Response
  – Exposure Assessment
  – Risk characterization
    • Risk Communication
    • Decision-making
    • Risk Management
• Use of Monte-Carlo modeling
Monte Carlo Simulation (MCS)

- Computerized mathematical technique: simulation
- One simulation run selects one value at random from each input distribution, calculates an outcome and stores it
- Repeats many times, each run generating a different result
- All results together generate a probability distribution
- The MCS generated a distribution of outcomes that modeled the probability of an infected RBC unit being transfused in the U.S.

Stanislaw Ulam

\[ \text{Food Intake } \times \text{ Contaminant Level} = \text{Exposure} \]
Quantitative Risk Assessments for vCJD in Blood Components

• FDA model

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/TransmissibleSpongiformEncephalopathiesAdvisor yCommittee/ucm339920.htm

• UK model

## Modeled U.S. Risk of vCJD from RBC Mean (2.5th-97.5th percentile)

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<tbody>
<tr>
<td></td>
<td>Infections</td>
<td>Clinical cases</td>
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<tr>
<td>Low UK prevalence (1.7 infections per million)</td>
<td>1 in 134 million (0 to 1 in 8.7 million)</td>
<td>0 (0-0)*</td>
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<tr>
<td>High UK prevalence (493 infections per million)</td>
<td>1 in 480,000 (1 in 4.3 million to 1 in 111,000)</td>
<td>6 (0-27)</td>
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*The 2.5th and 97.5th percentiles of (0-0) indicate that in at least 97.5 percent of the outputs generated by the model the estimated risk was zero.*
• Regulation is an essential element of any national or regional blood system to ensure appropriate standards
• Regulatory decisions take place in a larger societal context that governs acceptance of risks and costs
• The principles of risk-based decision making are well-established, but difficult to apply in the context of blood
  – The “precautionary principle” should not be applied without consideration of basic caveats
Summary - II

• A structured decision making process should include risk assessment, risk management, and risk communication
  – Ongoing scientific input is essential
  – There must be consideration of relative risks and benefits

• Decision making should be transparent
  – Acceptance of risk is a societal decision
  – Acceptance of cost is a societal decision

• Blood safety decisions have an international context
  – Decision makers should communicate the scientific, economic and societal basis of blood safety decisions
Summary - III

• EIDs continue to present challenges in blood safety regulation due to the cost and complexity of interventions
• Efforts are ongoing to develop a standardized framework for risk-based decision making that would improve coherence, but allow for different outcomes in various jurisdictions
• Increasingly, blood regulators are utilizing formal risk assessment tools in decision making
  – To estimate and address uncertainties
  – To quantify relative risks and benefits