Pathogen Inactivation and Blood Safety in the US

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Conflict of Interest

The American Red Cross is participating in a clinical trial of the Intercept pathogen inactivation process under IDE in Puerto Rico.
The Safety of the Blood Supply — Time to Raise the Bar

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Summary

• US blood collectors are facing unprecedented competitive challenges with commoditization of blood products and diminished reserve to address safety challenges.

• Unlike other countries, risk-based decision making by individual blood operators is currently not feasible due to the competitive environment.

• The US blood industry cannot develop and implement additional safety advances in the current economic situation without mandated implementation and clear, immediate reimbursement mechanisms.

• There is a need for timely and decisive actions from all stakeholders to protect patients.

• Additional mandated layers of safety are needed, including pathogen inactivation technologies.
The US Blood System

- American Red Cross
- Blood Systems Inc
- One Blood
- New York Blood Center

~ 67 independent blood centers
~ 200 hospital self collectors

- All are “not-for-profit”
- Regulated by the US Food and Drug Administration
- Blood is paid for through individual hospital contracts in a competitive market environment
- Safety is paid for out of blood operators margins

~50% of the blood supply
Blood Safety is a Joint Responsibility

- All participants share a joint responsibility in ensuring the safety of the US blood supply
- No single group or agency has a comprehensive ability to assure blood safety
- With changes over the prior decade, it is now unclear whether the US has an effective decision making process for blood safety
US Blood Policy

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

CHARTER

ADVISORY COMMITTEE ON BLOOD AND TISSUE SAFETY AND AVAILABILITY

DESCRIPTION OF DUTIES

The Committee will provide advice on a range of policy issues to include: (1) identification of public health issues through surveillance of blood and tissue safety issues with national biovigilance data tools; (2) identification of public health issues that affect availability of blood, blood products, and tissues; (3) broad public health, ethical and legal issues related to the safety of blood, blood products, and tissues; (4) the impact of various economic factors (e.g., product cost and supply) on safety and availability of blood, blood products, and tissues; (5) risk of infections to the health care workforce from transfused blood products and blood product raw materials; (6) development of universal protocols for identification, tracing and recall of blood products; (7) management of blood donation programs; (8) management of laboratory testing for blood donors, recipients and patients; (9) evaluation of current and future technologies to improve diagnostic accuracy of blood safety and availability; (10) development of guidelines to improve public confidence in the safety of blood products.
The Historical State

• A transfusion transmitted disease would be recognized by the community
• Companies would work with the Red Cross (and some other blood centers) to develop a screening test
• Red Cross would perform testing under IND and then continue testing until FDA approval
• Red Cross (and some independent centers) would implement universal screening on FDA approval of the test, often without immediately passing costs onto customers
• Two to four years later FDA would recommend or mandate the test and other blood centers would be obliged to implement
RBC Transfusions in the United States

Data derived from National Blood Collection and Utilization Surveys

RBC Transfusions (millions)

- 48.9 RBC/1,000
- 39.6 RBC/1,000
- 40.0 RBC/1,000

Year % Change
- 1994: 40.0 RBC/1,000
- 1997: 40.0 RBC/1,000
- 1999: 40.0 RBC/1,000
- 2001: 40.0 RBC/1,000
- 2004: 40.0 RBC/1,000
- 2006: 40.0 RBC/1,000
- 2008: 40.0 RBC/1,000
- 2011: 40.0 RBC/1,000
- 2012: 40.0 RBC/1,000
- 2013: 39.6 RBC/1,000
- 2014: 39.6 RBC/1,000
- 2015: 39.6 RBC/1,000
- 2016: 39.6 RBC/1,000
- 2017: 39.6 RBC/1,000
- 2018: 39.6 RBC/1,000
- 2019: 39.6 RBC/1,000
- 2020: 39.6 RBC/1,000
Blood Centers

- >20% decline in blood use in the US since 2008 has lead to intense competition between centers
- Red cell price has fallen due to oversupply in the face of diminished demand
- Blood centers are struggling financially, with >50% of the blood supply produced by centers with negative margins in 2013
- Americas Blood Centers (ABC) reports a reduction from 87 centers to 68, mostly due to mergers*
- Centers are reducing staff, closing facilities and decreasing investment in research
- In the face of intense competition, no individual center can introduce the additional costs of safety interventions without reimbursement

* New York Times, August 22, 2014
American Red Cross

- We can no longer afford to perform testing without reimbursement
- In future, we will work with test manufacturers to develop tests, but are likely to stop testing once IND work is complete unless hospitals are prepared to pay under cost recovery policies
- We are unlikely to initiate universal testing on FDA approval of a test, unless most other blood centers initiate testing at the same time and the hospitals will bear the costs
- Absent reimbursement, we are likely to wait for a FDA mandate before initiating universal screening tests
Test Manufacturers

- Uncertainty and delay around testing mandates creates untenable risk for companies investing in this area.
- Testing companies no longer view developing tests for the voluntary blood supply as commercially viable.
- Companies are especially unable to invest in selective testing models, e.g., dengue, chikungunya and babesia.
- Companies are moving offshore or into private equity.
- The US blood supply can no longer rely solely on industry innovation to support blood safety.
Accrediting Agencies: AABB

Association bulletins becoming less directive:

- **TRALI**  
  AB 06-07 - “blood centers should implement”

- **Young donors**  
  AB 08-04 - “may find this information useful”

- **Bacteria**  
  AB12-04 - “should develop policies”

- **Dengue**  
  No bulletin

- **Chikungunya**  
  AB 14-03 - “facilities consider recalling…”

- **Babesia**  
  AB14-05 - “should consider ...interventions”
Hospitals

• Reimbursement is disconnected from the price of blood and the costs of safety
• Hospitals, in general, will only pay for FDA mandated tests and often view safety recommendations as research that they are not obligated to support
• Hospitals are free to purchase blood from the lowest cost provider causing intense competition between blood collectors, inhibiting cost increases incurred by safety innovations
• Basing safety decisions on hospitals willingness or ability to pay leads to sporadic, uneven implementation
• This is not a viable strategy to protect patients or blood donors
Payors

• The payors do not participate in safety decisions and make no allowance for non-mandated tests
• Funding channeled to hospitals does not necessary flow to blood collectors, as hospitals receive market basket reimbursement under DRGs and negotiate blood prices independent of reimbursement
• There is no reimbursement process to support safety innovations
FDA

- There may be many years between BPAC recommendations, approval of a new test, publication of draft guidance and then final guidance
- BPAC recommendations and draft guidances are non-binding (except when they cite regulations)
- With respect to emerging issues and given other changes in the industry, the guidance process may be an ineffective mechanism to ensure safety in real time
The US Safety Conundrum

- FDA regulation and enforcement have effectively driven the development of high quality products and processes.
- In blood centers, the focus on cGMP and financial constraints have diminished our capacity to respond proactively to safety issues, e.g., by decreased R&D capacity.
- The FDA has approved multiple safety technologies that have not been implemented due to cost constraints.
- Blood safety in the US is now determined by hospital ability or willingness to pay.
- This has led to variability in blood safety across the US, e.g., leukoreduction, babesia screening, bacterial screening, etc.
The US Safety Conundrum II

• Regulation is now the only consistent method to drive implementation of safety innovations in the US
• The FDA needs to take proactive and timely steps to protect patients through direct mandates after appropriate stakeholder engagement
• Safety system that are not mandated are not safety systems
• In the absence of future investment in innovation, additional layers of safety are immediately necessary
• Pathogen inactivation provides an additional layer of safety that diminishes the need for rapid and immediate interventions
Additional Layers of Safety

Biopharmaceutical Pathogen Reduction/Clearance Technology

- Product NAT
- Nanofiltration
- Affinity Purification
- Solvent-Detergent
- AHF Heat
- Low pH
- UV/Propiolactone
- Fractionation
- Pasteurization

No HIV, HBV, HCV Transmissions since 1987

No WNV
No Dengue
No Chik

1985 2000 2010

Thanks to Harvey Klein MD
Pathogen Inactivation for Plasma

- Intercept\textsuperscript{\textregistered} system for plasma FDA approved in Dec. 2014
- Octaplas\textsuperscript{\textregistered} FDA approved in Dec. 2013
- Neither system is required nor is in widespread use
- Plasma is the highest window risk for HIV, hepatitis B & C when used with NAT testing, due to volume
- 4/6 US NAT non-reactive HIV transmissions due to plasma
- “Two FFP units and all three WB–derived PLT concentrates … were infectious, but three of nine (33\%) RBC concentrates … were not infectious*”
- 12 of 18 HBV transmissions were plasma or platelets*
- With relaxation of MSM criteria, pathogen inactivation of plasma would substantially reduce current window period risks and balance theoretical additional risks

*Kleinman et al Transfusion 2009:49; 2454
Safety Systems for Platelets

FDA approved safety systems for bacterial contamination include:

- Verax PGD point of issue test
- Immunetics BacTx point of issue test
- Cerus Intercept pathogen inactivation

None of these technologies is required or widely used. Bacterial sepsis and fatality remain a major risk. The Red Cross, ABC and AABB have called for mandated use of at least one of these technologies in addition to primary bacterial culture screening.
Conclusions

• The US Transfusion Medicine industry has diminishing economic ability to implement new safety initiatives without direct reimbursement
• The US has come full circle, where safety decisions are now based on hospital ability or willingness to pay
• There is a need for timely and decisive action to protect patients and donors
• The FDA should mandate approved safety innovations in a timely fashion
• Pathogen inactivation systems should be mandated in the US as an additional layer of safety and financial resources made available to fund implementation