



ELSEVIER

DRUG DISCOVERY
TODAY
TECHNOLOGIES

Editors-in-Chief

Kelvin Lam – Harvard Stem Cell Institute, Harvard University, USA

Henk Timmerman – Vrije Universiteit, The Netherlands

Critical path

Blood safety: Opportunities and challenges addressed through Critical Path research at FDA

Chintamani D. Atreya*, Jay S. Epstein

Office of Blood Research and Review, Center for Biologics Evaluation and Research, US Food and Drug Administration, Rockville, MD 20852, USA

New scientific discoveries and technologies create opportunities for medical and public health advancement through development of innovative products. However, novel products and technologies bring new challenges to regulation. FDA recently established a 'Critical Path' research initiative to modernize regulatory science concepts and tools to meet the challenges of the 21st century. Central to this initiative is the concept that regulatory science is distinct from the 'discovery' science that generates ideas for development of new drugs, biologics, or medical devices. In this article, the authors discuss the concepts of FDA 'Critical Path' research and review examples of such research performed in the Office of Blood Research and Review within the Center for Biologics Research and Evaluation at FDA to illustrate how the 'Critical Path' research is being used to address opportunities and challenges impacting blood and blood products.

Introduction: The FDA Critical Path research initiative

In recent years, the FDA has identified a compelling need to modernize the technologies and methodologies that we use to evaluate medical product safety, efficacy and quality as products move from the bench to the bedside in the 21st century. This modernization rests on the realization that the

Section Editor:

Janet Woodcock – Food and Drug Administration, Rockville, MD, USA

'regulatory science' that enables us to evaluate and predict product safety, efficacy and consistency in manufacturing is distinct from the 'discovery science' that generates new ideas for development of a drug, biologic, or a medical device, and requires its own scientific focus. Regulatory science is complementary to translational research, and its advancement is expected to facilitate the availability of new and safer products by removing barriers that arise from scientific uncertainty in making regulatory assessments.

The role of Critical Path research at FDA is to provide a current scientific framework for regulatory actions including risk assessment and communication, establishment of product standards and review practices, and development of guidance for industry. Research conducted within FDA plays an essential role in advancing Critical Path science because of the unique position of the Agency as a party motivated solely by the public health mission, neutral to commercial interests, and with access to a range of scientific information that spans the array of related products on the market or in pursuit of market approval. This position enables FDA to identify scientific gaps and cross-cutting issues as appropriate early in product development and to accelerate progress by making FDA's research findings publicly available including to all product sponsors without disclosing sponsors' proprietary and confidential information. Additionally, the laboratory research infrastructure within FDA can provide support and

*Corresponding author: C. Atreya (chintamani.atreya@fda.hhs.gov)

coordination of a larger Critical Path research effort across government, industry and academia.

In March 2004, the Agency published a document entitled 'Challenge and Opportunity on the Critical Path to New Medical Products' in which it called for a nationwide effort to modernize the critical path sciences. FDA then identified specific Critical Path opportunities through extensive outreach to the pharmaceutical industry, academia, patient groups, health-related organizations and other federal agencies. Subsequently, in March 2006, FDA published a follow-up report entitled 'Critical Path Opportunities Report and List' that identified 76 opportunities that would help FDA to modernize its CP sciences. In follow up, FDA published a list of more than 40 Critical Path research activities and collaborations that were initiated during 2006. These research activities were organized under six priority topics as follows [1]:

- Better Evaluation Tools
- Streamlining Clinical Trials
- Harnessing Bioinformatics
- Moving Manufacturing into the 21st Century
- Developing Products to Address Urgent Public Health Needs
- Specific At-Risk Populations – Pediatrics

Critical Path challenges and opportunities in blood product safety and efficacy

Within the Center for Biologics Research and Evaluation (CBER) at FDA, the Office of Blood Research and Review (OBRR) is responsible for ensuring the safety of the nation's blood supply by minimizing the risks of infectious disease transmission and other, non-infectious, hazards, while facilitating the maintenance of an adequate supply of blood and blood products. Furthermore, the Office develops and enforces quality standards, monitors, analyzes and, as needed, acts on reports of biological product deviations as a result of unexpected or unforeseeable events in manufacturing as well as adverse clinical events and performs specific investigational laboratory tests as needed to ensure nation's blood and blood products safety and availability.

Although these responsibilities of OBRR have supported regulatory advances in blood product safety and efficacy for many years, certainly focusing on Critical Path science as a discipline has provided new opportunities to address emerging challenges in blood safety. Under this new focus, based on current and anticipated scientific needs, OBRR has identified six high priority areas for research by analyzing recent product approval submissions and public health needs, and where the output could lower regulatory barriers to product development, or improve product safety, efficacy, consistency and availability. The priority areas are:

1. Development of predictive models for preclinical evaluation of blood components, blood derivatives and their analogues, including blood substitutes, and to study pathogenesis of blood borne emerging infectious agents.
2. Multiplex platforms and high-sensitivity methods for pathogen detection, including genetic variant emerging infectious diseases and bioterrorism agents.
3. Development of infectious agent panels for assay standardization and standards and reagents for product lot release testing.
4. Novel methods of pathogen reduction and inactivation in blood and blood products.
5. Development of methods to evaluate efficacy of immune globulins of bioterrorism and pandemic importance.
6. Development and evaluation of proteomics-based and genomics-based biomarkers for efficacy, quality, toxicity and consistency of blood components and blood derived products and their analogues, including blood substitutes.

To illustrate the opportunities and challenges addressed through FDA Critical Path research in the six identified priority areas for OBRR, here we briefly introduce to the readers with some of the examples of priority area research projects in OBRR.

Animal models and biomarkers to predict safety of modified hemoglobin (Hb) solutions as candidate oxygen carrying therapeutics

Solutions of hemoglobin-based oxygen carriers (HBOCs) potentially could serve as therapeutics with great potential to advance medical care as in many medical settings, including trauma resuscitation. However, all products studied to date have been highly toxic, and studies in animals have not been predictive of product safety or efficacy in clinical trials [2,3]. Therefore, identification of more suitable animal models and biomarkers predictive of HBOC product safety in humans are critical to enhance the success of the medical care to patients. Under the Critical Path research initiative, OBRR scientists have contributed significantly to the scientific understanding of HBOC toxicity related to binding of nitric oxide, blocking blood vessel relaxation, and disseminated vascular injury from oxidative reactions. Additionally, these scientists recently delineated the structural basis for lack of efficacy of a particular HBOC, and have identified guinea pigs rather than rats as a more suitable model for toxicity studies of HBOCs (For details of these novel studies readers are referred to refs [4,5]).

Investigations of prototype microarray and nanoparticle-based multiplex and high-sensitivity methods for detection of pathogens in donated blood

Blood and plasma donors are routinely screened for several transmissible agents and application of newer detection

technologies has continuously advanced blood safety. For example, the implementation since 2000 of nucleic acid amplification tests (NAT) for human immunodeficiency virus-1 (HIV-1) and hepatitis C virus (HCV) has significantly reduced the risk of transfusion transmission of these viruses compared with conventional serological test methods. Additionally, adaptation of NAT platforms for HIV-1 and HCV permitted the rapid development of donor screening tests for West Nile virus less than a year after a massive US epidemic emerged in 2002. However, the cost and complexity of an ever-increasing number of donor screening tests has led to the goal for development of screening test methods that can detect multiple infectious agents in a single test. Additionally, there is a recognized need to develop test platforms that can be rapidly adapted for detection of emerging infectious disease agents, including potential bioterrorism agents, of concern to blood safety. Such platforms also might allow detection of multiple potential bioterrorism (BT) agents as point-of-care diagnostics. To better understand the scientific barriers for regulation of candidate multiplex screening assays, OBRR scientists have experimented with a prototype microarray-based multiplex assay for the simultaneous detection and discrimination of hepatitis B and C, human immunodeficiency virus type-1 (HIV-1), and a variety of candidate bioterror agents in human blood samples [6]. Similarly, studies have been done to characterize the performance of a nanoparticle-based biobarcode amplification assay (BCA) method for HIV-1 capsid (p24) antigen detection. Preliminary evaluations have suggested that the HIV-1 p24 antigen BCA may provide a sensitive tool for early detection HIV-1 infection as an alternative to HIV-1 RNA testing by NAT in some settings [7].

Methods to improve West Nile virus detection to enhance blood safety

West Nile virus (WNV) is transmissible by blood transfusion, and our nation's blood supply is currently screened for the virus. However, there are cases in which WNV at low levels in a donor sample has failed to be detected, and the donated products have transmitted WNV disease to recipients. Troubled by this observation, an OBRR scientist has determined that a major proportion of WNV in blood samples is bound to red blood cells and therefore not measured by NAT performed on plasma samples. This finding opens the possibility that risk of WNV transmission from transfusion might be further reduced if NAT methods are adapted for use on donor samples of whole blood instead of plasma [8].

Detection and elimination of transmissible spongiform encephalopathy (TSE) agents in biological products

Several TSE agents cause fatal brain diseases in humans that have been transmitted by biological products of medical importance including human pituitary-derived hormones,

Dura mater grafts, corneal transplants, and transfused human blood, in addition to some surgical devices (re-used deep EEG electrodes). For this reason, studies in the areas of sensitive detection methods and effective removal and decontamination procedures for TSEs in biologics are a high priority for FDA Critical Path research. Scientists in OBRR are evaluating products under development for detecting latent human and animal infections with TSE agents. Such tests might serve as screens to reduce the TSE risk from vaccines, human cellular and tissue products and blood products. Studies also are being done to evaluate the susceptibility to TSE infection of different types of cells currently in use or proposed for use to manufacture vaccines and other biologics. Additionally, the ability of various manufacturing processes and decontamination methods to eliminate TSE infectivity is being evaluated [9,10].

Animal models for efficacy of immune globulins as for disaster preparedness and as bioterrorism countermeasures

In the event of a smallpox outbreak from bioterrorism intravenous preparations of vaccinia immune globulin (VIGIV) will be needed to prevent and treat known life-threatening complications of smallpox vaccination (with vaccinia virus) in susceptible individuals. However, efficacy of VIGIV to prevent and treat life-threatening complications of vaccinia in immunodeficient and eczematous individuals cannot be tested in humans. To address this issue, in a collaborative study, scientists at OBRR identified that intravenous immunoglobulin (IGIV) products contain neutralizing antibodies to vaccinia [11] and developed SCID mouse models in which the potency of candidate VIGIV preparations could be demonstrated. These models provided a pathway for licensure of new VIGIV products and additionally enabled the scientists to provide guidance on donor management following smallpox [12]. Our scientists are continuing to develop refinements to the animal models. Similar efforts are in progress to develop pathways for development of immune globulin products for use in pandemic influenza, anthrax and other disaster scenarios.

Conclusions

FDA plays a unique role in medical product development through science led regulation. Since 2004 the FDA's Critical Path initiative has focused attention on modernizing the methods and tools of regulatory science to meet the challenges of product development in the 21st Century. Within FDA, OBRR is actively engaged in Critical Path research related to safety, efficacy and quality of blood and blood products that contributes to advancements in patient care and public health.

Acknowledgement

We thank Dr Kathryn Carbone, Associate Director for Research, CBER, FDA for her review of this report and helpful critiques.

References

- 1 FDA's Critical Path Web page: <http://www.fda.gov/oc/initiatives/criticalpath/opportunities06.html>
- 2 Sloan, E.P. *et al.* (1999) Diaspirin cross-linked hemoglobin (DCLHb) in the treatment of severe traumatic hemorrhagic shock: a randomized controlled efficacy trial. *J. Am. Med. Assoc.* 282, 1857–1864
- 3 Kim, H.W. and Greenberg, A.G. (2004) Artificial oxygen carriers as red blood cell substitutes: a selected review and status. *Artif. Organs* 28, 813–828
- 4 Alayash, A.I. *et al.* (2007) First-generation blood substitutes: what have we learned? Biochemical and physiological perspectives *Exp. Opin. Biol. Ther.* 7, 665–675
- 5 Buehler, P.W. *et al.* (2007) Effects of endogenous ascorbate on oxidation, oxygenation and toxicokinetics of cell-free modified hemoglobin after exchange transfusion in rat and guinea pig. *J. Pharmacol. Exp. Ther.* [Epub ahead of print]
- 6 Hsia, C.C. *et al.* (2007) Microarray multiplex assay for the simultaneous detection and discrimination of hepatitis B, hepatitis C, and human immunodeficiency type-1 viruses in human blood samples. *Biochem. Biophys. Res. Commun.* 356, 1017–1023
- 7 Tang, S. *et al.* (2007) Nanoparticle-based biobarcode amplification assay (BCA) for sensitive and early detection of human immunodeficiency Type 1 capsid (p24) antigen. *J. Acq. Immune. Def. Syndr.* 46, 231–237
- 8 Rios, M. *et al.* (2007) West Nile virus adheres to human red blood cells in whole blood. *Clin. Infect. Dis.* 45, 181–186
- 9 Minor, P. *et al.* (2004) Standards for the assay of Creutzfeldt-Jakob disease specimens. *J. Gen. Virol.* 85, 1777–1784
- 10 Farshid, M. *et al.* (2005) Clearance of viruses and transmissible spongiform encephalopathy agents from biologicals. *Curr. Opin. Biotechnol.* 16, 561–567
- 11 Goldsmith, J.C. *et al.* (2004) Intravenous immunoglobulin products contain neutralizing antibodies to vaccinia. *Vox. Sang.* 86, 125–129
- 12 Guidance for Industry: Recommendations for Deferral of Donors and Quarantine and Retrieval of Blood and Blood Products in Recent Recipients of Smallpox Vaccine (Vaccinia Virus) and Certain Contacts of Smallpox Vaccine Recipients – 12/30/2002 – (Modified 2/4/2003) – (PDF), (Text), and accompanying Questions and Answers on FDA Guidance Entitled 'Recommendations for Deferral of Donors and Quarantine and Retrieval of Blood and Blood Products in Recent Recipients of Smallpox Vaccine (Vaccinia Virus) and Certain Contacts of Smallpox Vaccine Recipients'