fresh-frozen plasma (FFP) are completed; this product is approved in Europe and is now being used in two countries. Although PI of RBCs is technically more difficult and some methods were hampered by the development of antibodies in recipients, methods for PI of RBCs are under active study and may be available for implementation in coming years.

OTHER ISSUES CONSIDERED BY THE PANEL

Noninfectious hazards of transfusion

The panel recognized that the noninfectious hazards of transfusion such as TRALI and mistransfusion are more prevalent than currently recognized transmissible diseases and that PI does not address these problems. The panel did not believe that this issue should delay or inhibit the adoption of PI when the technology is ready. The panel urged that blood suppliers continue efforts to reduce these noninfectious complications but points out that the introduction of PI technology is not mutually exclusive of these efforts.

Rare risks

One concern with PI may be of a rare risk that would not be manifest until PI blood components have been transfused to a large number of patients. Although this problem may seem unique to PI, it really is not. Clinical trial data for licensure of any drug, biologic, or device will never be sufficiently extensive to identify very rare complications. The FDA must take rare risks into consideration with any drug, biologic, or device they license. Unfortunately, the United States does not have an effective system for postmarketing studies based on prelicensure data.[16] As the panel points out, this is the "weakest link in the regulatory process." They propose that licensure of PI mandate postmarketing studies as a condition of approval and that these studies might be somehow integrated with developing hemovigilance programs. An additional approach might include use of the RADAR project, which identifies previously unrecognized adverse drug and device reactions.[17] Follow-up of patients receiving amotosalen PI PLTs is linked with some hemovigilance programs in Europe.

Costs

The panel did not address the costs of implementing PI technology. They recommend that economic evaluations of PI should be carried out but emphasized that adoption of PI should be based on "considerations in addition to the results of an economic analysis."[1] Costs are "just one factor" in considering the use of PI. As the panel points out, many (most??) of the steps taken over the past two decades do not conform to the concepts of cost effectiveness used in other areas of medicine and health care. In the discussion of cost, the panel emphasized the importance of maintaining public confidence in the safety of the blood supply. This combined with the precautionary principle is consistent with other decisions regarding blood safety made over the past two decades and argues for the introduction of PI.

PI might not be as costly as some critics fear. In addition to elimination of the patient care costs of the diseases transmitted, transmission of agents not now tested should be prevented and those patients spared new infections. In the future, the countless hours spent in developing strategies to deal with new agents would be avoided and the costs of testing and loss of donors due to false-positive screening tests or medical history questions would be eliminated. In addition, irradiation of blood products, testing for bacterial contamination of PLTs, and testing for CMV and WNV could probably be eliminated; implementation of a test for trypanosomiasis could be avoided; and 7-day storage of PLTs could be reconsidered. Because plasma is replaced with a PLT additive solution during the amotosalen and potentially the riboflavin PI process, more plasma would become available for fractionation, thus providing some revenue. Because plasma is removed and because PI stops cytokine synthesis, transfusion reactions to PLTs should be decreased,[18] thus improving patient care and reducing the costs of managing these reactions.

Implications for developing countries

PI is discussed here in the context of developed countries. In many parts of the world, blood safety and transfusion-transmissible infections are a much greater problem than in developed countries. It is hoped that as PI becomes more widely used, the technology could be made available in some practical way in parts of the world where it is currently difficult to obtain an adequate supply of safe blood.

Implications of widespread adoption of PI

The panel also addresses several practical issues in the implementation of PI such as the problem of dual inventories. The amotosalen method for PI of plasma and PLTs widely used in Europe is different from that company's method under development for RBCs. Thus, that combination would not provide a single system for PI of all blood components. The riboflavin technology can be used for PLTs, plasma, and RBCs, making a single procedure effective for all components. Although currently there is no single licensed PI system for all blood components, the

panel felt that this should not delay adoption of PI for some components if overall considerations warrant its use.

If some, but not all, of the same blood component is subjected to PI, a dual inventory would arise. Both whole blood–derived (buffy coat) and apheresis PLTs are approved for use in Europe, so a single inventory of all PI PLTs is available there. It will be difficult to create a single inventory of PLTs in the United States, however, because whole blood–derived PLTs produced by the PLT-rich plasma method have not been studied in clinical trials. It seems unlikely that the United States would convert to buffy coat PLTs to adopt PI because only about 26 percent of PLTs in the United States are prepared from whole blood.[19] This problem could create pressure to speed the conversion to apheresis PLTs, motivate the manufacturers to develop a method for PI of PLTs produced with the PLT-rich plasma method, or provide incentive for the production of buffy coat–derived PLTs in the United States (currently happening in Canada).

Patient selection issues

There is no evidence that components that have undergone PI pose a unique risk for any particular group of patients. The panel recommends that PI products be made available to all patients unless new data indicates an as yet unknown risk for specific patients. Thus, for instance, the panel concluded that there is no need to withhold PI components from neonates or pregnant women.

THE STAKEHOLDERS FOR OUR PI DELIBERATIONS

The panel recommends "broad public consultation" as part of the decision regarding adoption of PI. Stakeholders include industry, academia, the blood banking and/or transfusion medicine community including transfusion medicine physicians and leaders of blood supply organizations, physicians who use blood in their practice, regulators, and most of all patients.

Industry has done impressive work to develop PI technology and publicize their results. They have the responsibility to continue thorough, careful development of PI technology pursing appropriate safety and efficacy issues to produce a product that is helpful to patients and can be implemented into the blood supply system practically and realistically.

Academia also has a role. The companies developing PI technology do not have the breadth and depth of knowledge that exists in our universities. Thus, industry should avail themselves of this expertise and university scientists and physicians should collaborate when it is appropriate.

The blood banking and/or transfusion medicine community has the responsibility to consider PI with a view to the long-term future. Transfusion medicine physicians should have the patients' interest as their first priority. If PI improves transfusion therapy, which our European colleagues have concluded, then PI should be adopted more broadly. Leaders of blood supply organizations have the responsibility to consider PI with an open mind. The technology may be technically complex, but this issue should not deter us from being open to it. We have successfully implemented many complex technologies such as apheresis, radioimmunoassay, ELISA, and NAT. Thus, the consideration is whether it is time for a paradigm shift to further improve blood safety and, if so, whether PI is ready for adoption beyond Europe. PI may alter our current operations or be inconvenient, but these issues have been true of most improvements. Leaders of blood supply organizations have the responsibility to look beyond these short-term logistical issues.

Regulators play a key role in the evolution of PI. Their requirements must be consistent and based on scientifically sound and available data. It is essential that they speak with one voice and from a single point of view. It is reasonable to expect that they will look beyond the benefits of the elimination of existing transfusion-transmitted infections and take into account elimination of some current activities that may become redundant with PI introduction.

Physicians who use blood in their practice depend on those of us in the transfusion medicine and/or blood banking community to demonstrate leadership in providing high-quality transfusion therapy. Dialogue with and among these physician groups will be important to hear the concerns and questions of transfusing physicians, to educate them as to the benefits and unique aspects of PI products, and to determine the best ways to introduce PI blood components into clinical practice at the appropriate time.

Of course, the primary stakeholders are patients. They must be the focus of all of us in transfusion medicine and blood banking. It is our responsibility to provide adequate and safe transfusion therapy and to make available the appropriate blood products. To this end, we must ask the hard questions of the developers of PI, expect complete data and high-quality clinical trials, and be open to the introduction of technology that may be complex, challenging, or even disruptive to our present operations. If PI improves patient care, patients have a right to expect that we use our expertise and creativity to implement change.

CONCLUSIONS OF THE EDITORIALIST

The body of work to develop PI represents very substantial progress. PI is now widely used in Europe and has arrived at a point for realistic consideration in Canada and the

United States. I believe that the benefits of PI extend far beyond eliminating the small number of remaining infections from the traditional list of transfusion-transmitted infectious diseases such as hepatitis or HIV. The benefits include shortening the long list of other transfusion-transmitted infections that are not prevented by present technology or other methods of donor screening. The benefits will also be proven with emerging agents or changes in known agents such as SARS or Avian flu. In addition, irradiation of blood components could be eliminated, removing transfusion-associated GVHD as a lethal complication of transfusion. We are at the end of the usefulness of the present paradigm and must move to a new one. It is incumbent on all of us to consider PI in this broad context.

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研究報告の概要

○病原体不活化:新技術についての決断 コンセンサス会議報告
2007年3月29日～30日、カナダのトロントで、カナダ血液サービスとヘマ・ケベックが主催する病原体不活化(PI)に関するコンセンサス会議が開かれた。様々な分野の専門家9名で構成されたコンセンサス・パネルに対して提示された質問に回答する形で本報告はまとめられている。
近年の検査技術の発達により、現状の輸血感染症リスクは大変低く、PIを直ちに導入することは推奨しない。しかし、新興感染症のリスクは未知数であり、PIは予防手段として重要である。広範囲の病原体を不活化できる実現可能で安全な方法が確立されればPIを実施すべきである。
特に毒性の面では安全性と効果について厳格な基準を適用するべきである。各国の規制当局の間でデータを共有し、協力して取り組むことが望ましい。適切に計画された市販後調査も必要であり、副作用調査は全国的ヘモビジランスシステムと連携して行うべきである。
本格的な実施に先だって、安全性と効果に関するデータや採血・製造・保管など影響を受ける工程について、慎重に検討すべきである。患者や医師など関係者への十分な説明と、血液センターや病院などでの研修が必要である。最初は限定された地域でのパイロットプログラムとして導入すべきだろう。
不活化実施によって、現在行われている感染症検査など一部の安全対策を取りやめ、費用を削減できる可能性がある。
全ての血液製剤にPIを導入するためには、政府の支援と大規模な投資が必要である。

報告企業の意見	今後の対応
2007年3月29日～30日、カナダのトロントで行われた病原体不活化技術に関するコンセンサス会議の報告である。	日本赤十字社は8項目の安全対策の一環として不活化技術の導入について、各不活化技術の効果、血液成分への影響、製造作業への影響などの評価検討を行っている。細菌やウイルスを不活化する方策について今後も情報の収集に努める。

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」
合成血-LR「日赤」
照射合成血-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

CONFERENCE REPORT

Pathogen inactivation: making decisions about new technologies

Report of a consensus conference

Harvey G. Klein, David Anderson, Marie-Josée Bernardi, Ritchard Cable, William Carey, Jeffrey S. Hoch, Nancy Robitaille, Marco L.A. Sivilotti, and Fiona Smaill

Methods to remove and inactivate pathogens, used extensively in the manufacture of plasma protein fractions, have all but eliminated transmission of infectious agents by these products.[1] Technologies for reducing the risk of infection from single donor blood components have not been embraced as enthusiastically. Several methods have been introduced in Europe. Treatment with solvent/detergent (S/D) or methylene blue have both been applied to plasma components, and psoralen treatment of platelets (PLTs) has begun in several countries.[2-4] Although S/D-treated pooled plasma has been approved for use in the United States and Canada, none of these methods has been adopted for single-donor products in North America. Reasons for slow acceptance include 1) the current safety of the volunteer blood supply; 2) the success of surveillance and development of screening tests to deal with emerging pathogens; 3) the inability of current technologies to inactivate some agents such as spores, prions, and certain small nonencapsulated viruses; 4) concerns regarding remote risks from the residual chemical agents used during the pathogen inactivation (PI) process; 5) absence of any single method to treat whole blood or all components; and 6) the cost-effectiveness of these technologies especially compared to strategies to reduce noninfectious risks of transfusion.[5] The Canadian Blood Services and Héma-Québec, with support from the Biomedical Excellence for Safer Transfusion (BEST) Collaborative, organized a consensus conference entitled, "Pathogen Inactivation: Making Decisions About New Technologies," in Toronto, Ontario, Canada, March 29 through 30, 2007, to provide recommendations and guide decision-making in this area. The term "inactivation" was intended to include methods that reduce pathogen risk by any means, including physical removal.

The conference format was based on the model developed by the National Institutes of Health.[6] The steering committee was aware of the potential weaknesses of the consensus process and made every effort to minimize selection bias, particularly with respect to the choice of questions and panelists.[7] The Consensus Panel, selected by the steering committee, had been provided background materials regarding transfusion risk and PI technology as well as a series of six questions designed by the committee to focus debate on the major issues involving pathogen reduction of blood components. The Panel convened immediately before the conference to clarify objectives, principles, and roles. On the first conference day, invited experts made formal presentations on a variety of relevant topics including transfusion risks, inactivation technology, toxicology, regulatory approaches, risk analysis, and cost-benefit considerations. An open forum audience of approximately 270 international attendees participated. The audience and the nine-member independent Consensus Panel, which included a wide range of disciplines (transfusion medicine, hematology, epidemiology, microbiology, toxicology, critical care medicine, medical policy, and ethics) as well as a chronic transfusion

ABBREVIATIONS: PI = pathogen inactivation; WNV = West Nile virus.

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TABLE 1. Risk per unit of selected transfusion-transmitted pathogens

Pathogen	Component	United States	Canada	Europe
HIV	All	1:2,000,000	1:7,800,000	1:900,000-5,500,000*
HCV	All	1:2,000,000	1:2,300,000	1:2,000,000-4,400,000*
HBV	All	1:277,000	1 in 153,000	1:77,000-1,100,000*
WNV	All	1:350,000	Rare	No reported cases
HTLV-I and/or -II	RBCs and/or PLTs	1:3,000,000	1:4,300,000	Not tested
Bacterial transmission	RBCs	1:40,000-1:5,000,000		
Bacterial sepsis	PLTs	1:59,000 single-donor	1:41,000 single-donor	1:11,000 (pooled)
Malaria	RBCs	1:1,000,000-1:5,000,000	Three cases in 10 years	11 cases in 10 years

* Variation between low and medium endemic areas. Modified from Bihl et al.[21]

recipient had an opportunity to question the presenters and add comment. The Consensus Panel reconvened in the evening to address the conference questions and prepare recommendations that could be applied both in Canada and internationally. On Conference Day 2, the Panel's draft statement was presented in its entirety to the experts and the audience for public comment. The Panel finalized the statement within a few weeks of the conference. A preliminary report has been published.[8]

This final Consensus Panel report is based on the information provided to the panelists before and during the conference, a review of background literature, and continued postconference discussion. The Panel by intent did not address advantages, disadvantages, current status, or cost of specific inactivation and/or reduction technologies or commercial products, although data regarding several technologies and trials were provided as background reading and presented at the conference. Several published summaries are available.[5,9-11] The conference questions and conclusions are summarized below.

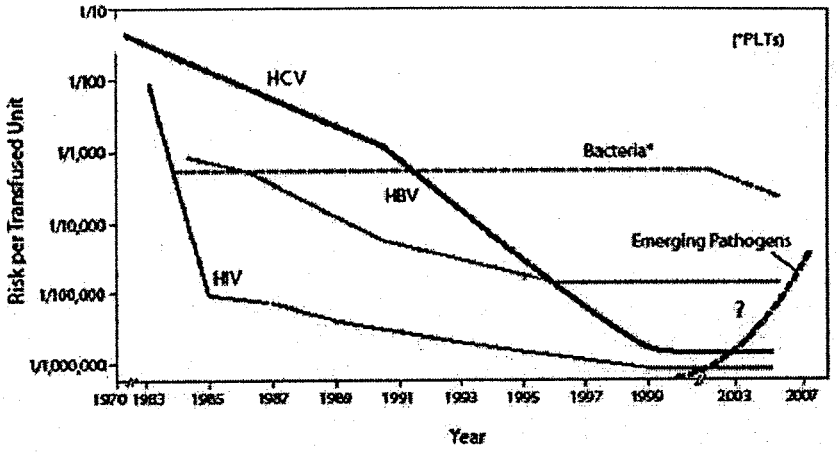

Fig. 1. Risks of transfusion-transmitted infections in the United States. Risk per unit transfused.

IS THE CURRENT RISK OF TRANSFUSION-TRANSMITTED DISEASES ACCEPTABLE IN RELATION TO OTHER RISKS OF TRANSFUSIONS?

Dramatic advances in the safety of allogeneic blood transfusion have been made during the past quarter of a century. At present, the estimated residual risk of transmission through transfusion of human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), and human T-lymphotropic virus (HTLV) in Canada is, respectively, 1 in 7.8 million donations, 1 in 2.3 million donations, 1 in 153,000 donations, and 1 in 4.3 million donations.[12] Risks still vary substantially even between low-endemic and high-endemic areas around the world (Table 1). For example, the residual risk of HBV per million blood donations is calculated to be 0.75 in Australia, 3.6 to 8.5 in the United States, 0.91 to 8.7 in Northern Europe, 7.5 to 13.9 in Southern Europe, and up to 200 in Hong Kong.[13-20] Nevertheless, the strategy of donor screening, testing, and deferral has proved remarkably successful in reducing the risk of transmission of the major viral pathogens (Fig. 1).[21]

Bacterial contamination of blood components was among the first recognized risks of transfusion.[22] The introduction of sterile interconnected plastic container systems and controlled refrigeration of blood components seemed to eliminate this risk by the 1960s; however, this conclusion proved illusory. Contamination of PLTs, the blood component stored at room temperature and therefore most susceptible to microbial growth, has been reported between 1 in 2000 and 1 in 5000 PLT collections (active surveillance in the United States) before the implementation of bacterial testing of PLTs, and bacterial sepsis has occurred on the order of 1 in 41,000 transfusions (voluntary reporting in Canada) after the introduction of screening cultures.[23-25] In the United States the frequency of septic reactions from single-donor (apheresis) PLTs before routine culture has been measured at 1 in 15,000 infusions.[26] Introduction of routine "in-process" culture of

PLTs has reduced the risk by about 50 percent. The American Red Cross now reports a residual risk of a septic transfusion reaction from a culture-negative single-donor unit at 1 in 50,200 (20 reported cases of sepsis including 3 fatalities associated with 1,004,000 single-donor PLT components tested).[27] These results are consistent with the Canadian experience. During the same period (2004-2006), septic transfusion reactions from whole blood–derived PLTs that were released without culture approached 1 in 33,000 (30 reported cases of sepsis in 1 million whole blood–derived PLT components released).[28]

Although Chagas disease, babesiosis, and West Nile virus (WNV) have been recent transfusion threats in the United States and Canada, published transmissions of other pathogens, such as hepatitis E and other viruses, other parasites, or prions that result in clinically important illness are very uncommon in the developed world.[21,29-31]

Hemovigilance data from developed countries suggest that the recognized noninfectious risks in aggregate are substantially higher than the current infectious risks of transfusion.[32] Transfusion-related acute lung injury (TRALI), which claims an estimated 50 to 100 lives in the United States each year, has been cited as the most frequent transfusion-related cause of death.[33,34] Acute transfusion reactions resulting from mistransfusion are fatal in about 1 in 1 million transfusions.[35] The frequency of acute and delayed hemolysis alone far exceeds that of clinically important pathogen transmission.[32] Based on the relatively low rates of existing infectious transfusion-related complications alone, the Panel does not recommend immediate introduction of PI with its attendant unknown risks. Even active surveillance, however, cannot estimate the risk of an emerging transfusion-transmitted pathogen. The Panel recognizes that such agents have been detected in blood donors at an increasing rate since the HIV epidemic.[36] The reactive strategy of surveillance, identification, test development, and screening permits a pathogen to disseminate widely even before clinical disease is recognized as was the case with HIV.[37] Furthermore, estimates presented at this conference by Dr Harvey J. Alter suggest that as many as 4.8 million cases of hepatitis, with an ensuing 768,000 cases of cirrhosis, resulted from transfusion in the 1970s and 1980s before a specific test for HCV was introduced. In addition to causing morbidity and mortality, the emergence of new pathogens also undermines public confidence in the blood supply. The Panel believes that such risks require a proactive approach in accordance with the precautionary principle (when facing public health threats for which the outcome can reasonably be predicted based, for example, on similar past issues, the precautionary principle dictates a risk assessment [which compares possible consequences of the action against the consequences of no action, according to available evidence and the rules of science], that favors a proactive approach, taking into account society's expectations that responsible actions be taken to circumscribe the threat. Under such circumstances, risks assessment that would favor inaction could be argued to be irresponsible and unethical, putting the public safety and the safety of future generations at greater risk. The active form of application of the principle places the burden of proof on those who propose a restrictive measure), which provides for a distinctive way of making decisions for managing serious threats to public health where there is scientific uncertainty to meet society's expectations that risks be addressed.[38,39]

If so, under what new circumstances should PI be implemented?

Given the recognition of transfusion-transmitted agents that are entering the blood supply and the risk of emerging infectious threats, the Panel believes that PI should be implemented when a feasible and safe method to inactivate a broad spectrum of infectious agents is available.

The Panel acknowledges that noninfectious hazards of transfusion can entail serious safety issues and deserve specific consideration. Blood services should direct attention to, and supply the necessary resources for, their resolution. For example, existing technology can provide a unified database for the patient's transfusion history, so that multiple collaborating hospitals could access patient blood type, antibody history, reactions to transfusion, and special transfusion needs in real time; one such system is operating in Quebec. Bedside bar-code systems and other technologic solutions have been introduced to improve positive patient identification and reduce transfusion errors.[40,41] The risk of TRALI can be reduced by excluding high-risk donors, limiting plasma use, and developing screening test technology.[34] All of these strategies are currently underfunded and underdeployed. A cost estimate by Dr Sunny Dzik presented to this conference, however, suggested that substantial risk reduction in TRALI and hemolytic transfusion reactions could be accomplished for $14 to $28 per unit, a sum that would raise the cost of blood in the United States by less than 10 percent (Table 2). Introduction of PI technology should not preclude vigorous efforts to reduce these noninfectious risks.

Should the criteria be the same for red cells, PLTs, and fresh-frozen plasma?

The same criteria of safety, feasibility, and efficacy should apply to all blood components. A single method for inactivating pathogens in all blood components would be ideal. No such system is likely to be introduced in the foreseeable future. The absence of an integrated system, however, does not imply that PI of any one component should be delayed until a method is proven satisfactory for all components.

TABLE 2. Costs to reduce noninfectious hazards*

Cost drivers	Patient bar code	Unified online database	TRALI: exclusion and/or HLA testing of high-risk donors	Total
Incremental cost/unit	$10-$20	$3-$6	$1-$2	$14-$28
× 27 million units†	$392 million	$90 million	$40 million	$432 million
Number of major events (hemovigilance data)†				295
Cost per event avoided				$1.5 million

* Adapted from S. Dzik as presented at Consensus Conference.
† Data from Stains by et al.[32]

Should different criteria be used for certain patient populations?

Once the decision has been made to move forward with a method for PI for a specific blood component, the treated product should be used universally. Traditionally, premature infants, children, and pregnant women have been considered "vulnerable populations." The same patients may be at particular risk for transfusion-transmitted pathogens, however, and might arguably derive special benefit from PI blood components. The Panel recognizes that there are few current data available on which to individualize risk-benefit assessment. For example, infection with HBV in infancy or early childhood may lead to a high rate of persistent infection (25%-90%) with significant morbidity.[42] Cytomegalovirus (CMV), in contrast, is readily transmitted by transfusion; however, infection does not necessarily result in increased morbidity and mortality, even for low-birth-weight and premature infants.[43] Similarly, blood component transmission of hepatitis C to neonates and children was common, but the epidemiologic data, histologic findings, and clinical outcomes are conflicting.[44,45] Even fewer data address the potential risk of trace amounts of residual additive, photoderivatives, or metabolites from the current inactivating agents. Until additional new information identifies groups of patients who should not receive the PI product, the Panel concluded that the product should be made universally available.

WHAT MINIMUM ACCEPTABLE SAFETY AND EFFICACY CRITERIA SHOULD BE PUT INTO PLACE FOR THE PREAPPROVAL ASSESSMENT OF PATHOGEN-INACTIVATED PRODUCTS? SPECIFICALLY:

What criteria should govern acceptable toxicology standards and how should they be assessed?

The Panel recognizes that the different regulatory authorities have established their own standard approaches to these assessments. Each agency has specific protocols and criteria for determining safety and efficacy. The Panel endorses the rigorous application of standards for safety and efficacy, particularly in the area of toxicology.[46,47] Established toxicology methods of systematically estimating hazards, anticipated exposure levels, and relevant dose-response relationships should be followed, to ensure a very high margin of safety for transfusion recipients. PI technologies that target nucleic acid should, for example, undergo careful scrutiny to assess the potential for genotoxicity, carcinogenicity, reproductive toxicity, and germline toxicity. These studies should be peer-reviewed and published.[48-50] The Panel strongly recommends that clinically relevant endpoints be selected when studying the direct toxicity of PI techniques on the blood product itself, rather than merely considering, for example, functional assays of oxygen delivery that have been proposed at this conference as one endpoint for evaluating PI of red cells (RBCs). The Panel recognizes that regulatory agencies may be constrained by issues of confidentiality in their ability to share proprietary information with the public.[48,49,51-53] The Panel encourages the harmonization of approaches and sharing of data among the various regulatory agencies internationally, however.[54]

What type of postmarketing surveillance should be required (if any) with the implementation of pathogen-inactivated blood components?

New drugs, biologics, and devices, such as modified blood components, blood containers, and anticoagulant-preservative solutions, undergo careful evaluations for efficacy and safety before approval. The premarketing randomized clinical trials are generally small, short-term studies that may fail to detect toxicities of low frequency (Table 3). New technologies are typically either approved or rejected based on these studies. In most countries, postapproval safety is monitored by a voluntary adverse event reporting system in which health-care professionals report adverse events thought to be related to the drug or biologic.[55] This collection of voluntarily submitted case reports represents the weakest link in the regulatory process. The Panel recognizes the difficulty of postmarketing surveillance studies.[56] Well-designed studies, however, should be mandated by the regulatory authorities and supported by the manufacturers and/or the blood