BIOVIGILANCE IN THE UNITED STATES: EFFORTS TO BRIDGE A CRITICAL GAP IN PATIENT SAFETY AND DONOR HEALTH

This report is a work product of the Public Health Service (PHS) Biovigilance Task Group in response to recommendations of the HHS Advisory Committee on Blood Safety and Availability

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UNITED STATES BIOVIGILANCE: EFFORTS TO BRIDGE A CRITICAL DONOR AND PATIENT SAFETY GAP

Table of Contents

Acknowledgements 2
Table of Contents 3
Abbreviations Used in this Document 7
1.0 EXECUTIVE SUMMARY 10
1.1 Issue 10
1.2 Objectives 10
1.3 Methods 10
1.4 Summary 11
1.4.1 Blood 11
Gap 1: Patchwork and sometimes fragmented system of various adverse event reporting 11
Gap 2: Likely under-reporting of transfusion adverse events 11
Gap 3: Challenges with FDA-required reporting 11
Gap 4: Need for accurate recipient denominator data, precise definitions, and training 11
Gap 5: No national surveillance of donor serious adverse events other than fatalities 11
Gap 6: Need for accurate donor denominator data, precise definitions, and training 11
Gap 7: Need for accurate tracking of all donor infectious disease test data 11
Gap 8: Need for timely analysis of reported data 11
1.4.2 Tissues 11
Gap 9: Limited information on the potential for HCT/Ps to transmit infectious disease 11
Gap 10: Ability to ascertain that reported infections in HCT/P recipients can be attributed to the tissue is limited. 11
Gap 11: Regulations concerning HCT/P adverse reaction reporting do not extend to the level of the healthcare facility or healthcare provider 11
Gap 12: Current mechanisms for tracking HCT/P grafts to the level of the recipient are limited. 11
Gap 13: Adverse reaction reporting for HCT/Ps regulated solely under Section 361 of the PHS Act is limited to infectious diseases 11
Gap 14: Information about adverse reactions in other recipients of HCT/Ps from an implicated donor may not be readily available 12
1.4.3 Organs 12
Gap 15: Lack of nationwide common organ/tissue donor network system for real-time reporting, data collection, communication, and

analysis of donor transmitted diseases in organ and tissue transplant recipients, including a common donor identifier necessary for linkage back to implicated donor of both organs and tissues. 12
Gap 16: No Requirement to retain donor and recipient samples 12
1.5 Recommendations: 12
2.0 BIOVIGILANCE IN THE UNITED STATES 13
2.1 Purpose 13
2.2 Background 13
2.3 Definition of Biovigilance 14
2.4 Surveillance: Sentinel Event Reporting vs. Adjusted Rate Benchmarking 15
3.0 GLOBAL MODELS OF COMPREHENSIVE HEMOVIGILANCE 16
Table 1. Comparison of adverse reporting requirement of countries represented in the European Haemovigilance Network (EHN) 17
Figure 1. Governance models of various hemovigilance systems in various countries 18
4.0 HEMOVIGILANCE EFFORTS IN THE UNITED STATES: A PATCHWORK OF BLOOD SAFETY PROGRAMS 20
4.1 Blood Recipients and Transfusion-Related Adverse Events 20
4.1.1 Federal Government Activities 20
Table 2. Donor, recipient, and linked donor-recipient repositories in the US. 25
4.1.2 Public/Private and Private Sector Activities 26
4.1.3 US Transfusion Hemovigilance Initiatives to Date 28
4.2 Gaps in Current US Transfusion Recipient Adverse Reaction Reporting Systems 29
Gap 1: Patchwork and sometimes fragmented system of various adverse event reporting 29
Gap 2: Likely under-reporting of transfusion adverse events 29
Gap 3: Challenges with FDA-required reporting 30
Gap 4: Need for accurate recipient denominator data, precise definitions, and training 32
Gap 5: No national surveillance of donor serious adverse events other than fatalities 33
Gap 6: Need for accurate donor denominator data, precise definitions, and training 36
Gap 7: Need for accurate tracking of all donor infectious disease test data 37
Gap 8: Need for timely analysis of reported data 38
4.3 Emerging Threat Assessment: Looking Beyond Known Transfusion-Related Events 38
4.4 A New Initiative: A Public-Private Partnership in Hemovigilance Surveillance Reporting 39
4.4.1 Public/Private Initiatives in Recipient Hemovigilance 40

4.4.2 Public/Private Initiatives in Donor Hemovigilance 41
4.4.3 Future Challenges, Including Integration of Private and Public Hemovigilance Efforts 42
Figure 2. The current patchwork of biovigilance 43
Figure 3. Portal concept of biovigilance reporting 44
Figure 4. Potential Model of Electronic Health Record (EHR) Exchange Interoperability 44
5.0 BIOVIGILANCE EFFORTS IN THE US: ADVERSE EVENTS ASSOCIATED WITH HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS 45
5.1 Background 45
Table 3. Federal Oversight/Regulation of Hematopoietic Progenitor Cells* 46
5.2 HCT/P Biovigilance Concerns 47
Figure 5. Tissue Donors Recovered in US in the first part of 21st Century 47
Figure 6. Musculoskeletal grafts distributed in US in the first part of 21st Century 48
5.3 Efforts in HCT/P Biovigilance 49
5.3.1 Global Biovigilance 49
5.3.2 HCT/P Biovigilance in the United States 50
5.3.2.1 Federal Reporting 50
5.3.2.2 Private Sector Reporting 53
5.4 Gaps in Current HPC/T Adverse Reaction Reporting Systems 55
Gap 9: Limited information on the potential for HCT/Ps to transmit infectious disease 55
Gap 10: Ability to ascertain whether reported infections in HCT/P recipients can be attributed to the tissue is limited. 55
Gap 11: Regulations concerning HCT/P adverse reaction reporting do not extend to the level of the healthcare facility or healthcare provider 55
Gap 12: Current mechanisms for tracking HCT/Ps to the level of the recipient are limited. 56
Gap 13: Adverse reaction reporting for HCT/Ps regulated solely under Section 361 of the PHS Act is limited to infectious diseases 56
Gap 14: Information about adverse reactions in other recipients of HCT/Ps from an implicated donor may not be readily available 56
6.0 BIOVIGILANCE EFFORTS IN THE US: ADVERSE EVENTS ASSOCIATED WITH SOLID ORGANS 57
6.1 Solid Organ Adverse Event Reporting 57
6.2 Gaps in Current Organ Adverse Reaction Event Reporting Systems 61
Gap 15: Lack of nationwide common organ/tissue donor network system for real-time reporting, data collection, communication, and analysis of donor transmitted diseases in organ and tissue transplant recipients,

including a common donor identifier necessary for linkage back to implicated donor of both organs and tissues 61
Gap 16: No Requirement to retain donor and recipient samples 62
7.0 POLICY CHALLENGES 64
7.1 Historical Background 64
7.2 Mandates for a Comprehensive Biovigilance Program 65
7.3 Mandatory vs. Voluntary Adverse Event Reporting 65
7.4 Public/Private Partnership 66
7.5 Conclusions 66
7.6 Recommendations 68
8.0 APPENDICES 69
APPENDIX 1: Blood Action Plan 69
FY98 69
FY99 70
FY00 71
FY01 72
FY02 72
FY04 73
FY05 73
FY06 73
FY07 74
FY08 75
APPENDIX 2: Office of the Secretary's Office of Public Health and Science Draft Strategic Plan 76
APPENDIX 3: Tissue Transplant Record (Northwest Tissue Services) 94
APPENDIX 4: NMDP Form 701 95
APPENDIX 5: NMDP Form 760 96
APPENDIX 6: Cell Therapy Adverse Event Form (University of California San Diego Medical Center) 97
9.0 References 98

Abbreviations Used in this Document

AABB	Formerly the American Association of Blood Banks
AATB	American Association of Tissue Banks
ABC	America's Blood Centers
ACBSA	Advisory Committee on Blood Safety and Availability
AE	Adverse Event
AERS	Adverse Event Reporting System
AHA	American Hospital Association
AHRQ	Agency for Healthcare Research and Quality
AIDS	Acquired Immunodeficiency Syndrome
ARC	American Red Cross
ASH	Assistant Secretary for Health
BASIS	Blood Availability and Safety Information System
BCP	Blood Centers of the Pacific
BPDR	Biological Product Deviation Report
BWG	Biovigilance Working Group
CAP	College of American Pathologists
CBER	Center for Biologics Evaluation and Research
CBS	Canadian Blood Services
CDC	Centers for Disease Control and Prevention
CDRH	Center for Devices and Radiological Health
CLIA	Clinical Laboratory Improvement Amendments of 1988
cGMP	Current Good Manufacturing Practice
cGTP	Current Good Tissue Practice
CIBMTR	Center for International Blood and Marrow Transplant Research
CMS	Centers for Medicare & Medicaid Services
DRCP	Donor and Recipient Complications Program
DoD	Department of Defense
DPSMC	Donor and Patient Safety Monitoring Committee
DRG	Diagnosis-related Groups
DTAC	Disease Transmission Advisory Committee
EBAA	Eye Bank Association of America
EC	European Commission
EHR	Electronic Health Record
EHN	European Haemovigilance Network
EID	Emerging Infectious Diseases
EUSTITE	European Union Standards and Training for the Inspection of Tissue Establishments
FACTS	Frequency of Agents Communicable by Transfusion Study
FD&C	Federal Food, Drug and Cosmetic Act

FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GLPR	General Leukocyte and Plasma Repository
GSR	General Serum Repository
GVHD	Graft Versus Host Disease
HBV	Hepatitis B Virus
HCT/P	Human Cells, Tissues, and Cellular and Tissue-based Product
HCV	Hepatitis C Virus
HHS	Department of Health and Human Services
HHV-8	Human Herpesvirus 8
HIV	Human Immunodeficiency Virus
HMO	Health Maintenance Organization
HPC	Hematopoietic Progenitor Cells
HRSA	Health Resources and Services Administration
HTA	Human Tissue Authority
IBMTR	International Bone Marrow Transplant Registry
IHN	International Haemovigilance Network
IND	Investigational New Drug
IRB	Institutional Review Board
ISBT	International Society for Blood Transfusion
LCMV	Lymphocytic Choriomeningitis Virus
MAB	Medical Advisory Board
MedSun	Medical Product Safety Network
MERS-TM	Medical Event Reporting System for Transfusion Medicine
NAT	Nucleic Acid Test
NBCUS	National Blood Collection and Utilization Survey
NCBI	National Cord Blood Inventory
NHLBI	National Heart, Lung, and Blood Institute
NHSN	National Healthcare Safety Network
NIH	National Institutes of Health
NMDP	National Marrow Donor Program
NOTA	National Organ Transplant Act
OARRS	Online Adverse Reaction Reporting System
OCTGT	Office of Cellular, Tissue and Gene Therapies
OBRR	Office of Blood Research and Review
OCBQ	Office of Compliance and Biologics Quality
OPDIV	Operating Divisions of the Department of Health and Human Services
OPTN	Organ Procurement and Transplantation Network
PBSC	Peripheral Blood Stem Cells
PDI	Post Donation Information
PHS	Public Health Service

PLT	Platelets
PPTA	Plasma Protein Therapeutics Association
PVD	Presumed Viremic Donors
RADAR	Retrovirus Epidemiology Donor Study Allogeneic Donor and Recipient
RBC	Red Blood Cells
REDS	Retrovirus Epidemiology Donor Study
RFID	Radio Frequency Identification
SAE	Serious Adverse Events
SENV	SEN virus
SHOT	Serious Hazards of Transfusions
SRR	Safety Reporting Rule
TACO	Transfusion Associated Circulatory Overload
TJC	The Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations [JCAHO])
TRALI	Transfusion Related Acute Lung Injury
TRIP	Transfusion Reactions in Patients
TSO	Transfusion Safety Officer
TSS	Transfusion Safety Study
TST	Tissue Safety Team
TTD	Transfusion Transmitted Diseases
TTVS	Transfusion Transmitted Viruses Study
UBS	United Blood Services
UCB	Umbilical Cord Blood
UK	United Kingdom
UNOS	United Network for Organ Sharing
US	United States
VCA	Vascularized Composite Allografts
vCJD	variant Creutzfeldt-Jakob Disease
WB	Whole Blood
WHO	World Health Organization
WNV	West Nile virus

1.0 EXECUTIVE SUMMARY

1.1 Issue

The Advisory Committee on Blood Safety and Availability (ACBSA) recommended in August 2006 that the Department of Health and Human Services (HHS) coordinate Federal actions and programs to support and facilitate biovigilance in partnership with private sector initiatives. The ACBSA has defined "biovigilance" as a comprehensive and integrated national patient safety program to collect, analyze and report on the outcomes of collection and transfusion and/or transplantation of blood components and derivatives, cells, tissues, and organs. The ACBSA recommended that biovigilance should be considered as a potential system to improve patient safety. They recommended that a biovigilance program should be outcome driven with the objectives of providing early warning systems of safety issues, exchanging of safety information, and promoting education and the application of evidence for practice improvement. The ACBSA further recommended that the government form a Biovigilance Task Group to perform a gap analysis of the current systems and make recommendations for a public-private partnership in biovigilance.

1.2 Objectives

The objectives of this report are to review current biovigilance efforts in the US and recommend a national plan for biovigilance in the future, including review of the current status of hemovigilance and biovigilance system infrastructure and gaps for blood; human cells, tissues, and cellular and tissue-based products; and organs. Finally, the report will conclude with a summary of system needs and recommendations for a national biovigilance plan, consistent with the charges given by ACBSA.

1.3 Methods

A comprehensive review of current surveillance and adverse event reporting systems for blood; human cells, tissues, and cellular and tissue-based products (HCT/Ps); and organs was undertaken by a task group of the Public Health Service (PHS) Biovigilance Working Group (BWG). This white paper review included relevant PHS agencies (Centers for Disease Control and Prevention, Food and Drug Administration, National Institutes of Health, and Healthcare Resources Services Administration and the Center for Medicare and Medicaid Services). The PHS BWG carefully considered the various roles and missions of the PHS agencies play in program oversight and product regulation.

1.4 Summary

The PHS BWG found in its review that at the present time, biovigilance in the US is a patchwork of activities, not a cohesive national program. Although this patchwork is functional, some of these activities are redundant, while others are limited in scope, resulting in inefficiency and gaps. Each HHS agency has created some means of data collection for outcomes and adverse events in support of its mission and objectives, including regulatory obligations. Professional organizations have also implemented standards for quality systems, which require investigation of adverse outcomes and errors. Recommendations on biovigilance systems and partnerships to fill existing gaps are complicated by the lack of a national policy and a pluralistic approach to the safety and availability of blood, tissue, and organs. Both voluntary and mandatory systems are needed. Integration of systems with both public and private sector support and joint governance of national biovigilance collaborative is vital.

1.4.1 Blood

Gap 1: Patchwork and sometimes fragmented system of various adverse event reporting
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Gap 4: Need for accurate recipient denominator data, precise definitions, and training
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Gap 8: Need for timely analysis of reported data

1.4.2 Tissues

Gap 9: Limited information on the potential for HCT/Ps to transmit infectious disease
Gap 10: Ability to ascertain that reported infections in HCT/P recipients can be attributed to the tissue is limited.
Gap 11: Regulations concerning HCT/P adverse reaction reporting do not extend to the level of the healthcare facility or healthcare provider
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Gap 14: Information about adverse reactions in other recipients of HCT/Ps from an implicated donor may not be readily available

1.4.3 Organs

Gap 15: Lack of nationwide common organ/tissue donor network system for real-time reporting, data collection, communication, and analysis of donor transmitted diseases in organ and tissue transplant recipients, including a common donor identifier necessary for linkage back to implicated donor of both organs and tissues.

Gap 16: No Requirement to retain donor and recipient samples

1.5 Recommendations:

1. We recommend government resource support for a national biovigilance program to monitor and enhance safety of blood, organs, and HCT/Ps.
2. We recommend integration of systems within the government and those within the private sector, involving blood, organs, and HCT/Ps, including all related voluntary and mandatory adverse event reporting systems.
3. We recommend steps to enhance mechanisms for surveillance, including sentinel reporting and investigation, and comprehensive surveillance that features benchmarking.
4. We recommend developing an HHS action plan to support the above three recommendations.

2.0 BIOVIGILANCE IN THE UNITED STATES

2.1 Purpose

The Advisory Committee on Blood Safety and Availability (ACBSA) recommended in August 2006 that the Department of Health and Human Services (HHS) Secretary coordinate Federal actions and programs within the United States (U.S.) to support and facilitate biovigilance in partnership with private sector initiatives. A PHS BWG was formed to identify the vision, goals, and processes needed to advance these objectives. The PHS BWG was charged with producing an analysis and operational report incorporating both public and private sector efforts to include:

- A gap analysis regarding the effectiveness of the current activities;
- The need for mandatory versus non-mandatory, and regulatory versus non-regulatory reporting;
- The scope of reporting with regard to product problems, medical errors and clinical adverse events including recognized and novel events;
- Database centralization versus data sharing;
- Database governance, ownership and accessibility;
- Format and standards for data reporting including confidentiality;
- Potential for coordination with non-US safety reporting systems;
- Funding mechanisms for a sustainable system; and,
- Design and feasibility of suitable pilot programs to determine the characteristics of a value-added system.

The objectives of this report are to review current biovigilance efforts in the US and recommend a national plan for biovigilance in the future. First, we will review the current status of hemovigilance and biovigilance system infrastructure and gaps nationally; global systems will also be briefly reviewed in order to provide perspective. The review will be separated into biovigilance systems for blood; human cells, tissues, and cellular and tissue-based products (HCT/Ps); and organs. Identification and analysis of system gaps will also be included for each section. Finally, the report will conclude with a summary of system needs and recommendations for a national biovigilance plan, consistent with the charges given by ACBSA.

2.2 Background

Advances in science and healthcare technology have led to more biologic products being collected to sustain and improve the quality of human life. In the United States (US) in 2007, over 30 million units of blood or blood products, 28,000 organs, and two million tissue allografts were transfused or transplanted. Despite these large numbers, demand often exceeds

availability, particularly for organs. Challenges exist to monitor and ensure appropriate access to and availability of safe products, both in the domestic and global arenas. Efforts to increase the availability of these products also may increase the opportunities for transmission of infectious pathogens, including viruses, bacteria, parasites and prions. These risks are multiplied when there are multiple recipients from a common donor. Examples of diseases or organisms transmitted through blood, organs, or other tissues include Human Immunodeficiency Virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), human T-cell lymphotrophic virus types I and II (HTLV-I/II), West Nile virus (WNV), rabies virus, lymphocytic choriomeningitis virus (LCMV), Group A Streptococcus, *Mycobacterium tuberculosis*, malaria, babesiosis, variant Creutzfeldt-Jakob Disease (vCJD), and *Trypanosoma cruzi* (the etiologic agent of Chagas disease). Transmitted malignancies have been reported primarily through organ transplantation. Beyond disease transmission, other concerns include adverse immunologic response, reaction to toxins, or decrease in expected function. These non-infectious events may be due to deficiencies in the product, or a mismatch between the product and recipient immunologic profile, but consequences may be as severe as for infectious disease transmission events.

Biologic-based products or technologies are likely always to carry an inherent risk. While solid organs cannot be altered to reduce infectivity, some tissues can be processed with chemicals or radiation, and blood can be modified, e.g. through leukocyte filtration or irradiation. However, no process can completely eliminate the inherent risks of transfusion and transplantation. The role of patient safety efforts is to drive that risk to the lowest level reasonably achievable without unduly decreasing the availability of these life saving resources, so that the overall benefit outweighs risk.

2.3 Definition of Biovigilance

The ACBSA has defined "biovigilance" as a comprehensive and integrated national patient safety program to collect, analyze and report on the outcomes of collection and transfusion and/or transplantation of blood components and derivatives, cells, tissues, and organs. The program should be outcome driven with the objectives of providing early warning systems of safety issues, exchanging of safety information, and promoting education and the application of evidence for practice improvement. Donor biovigilance is integral to the total biovigilance program since donors provide the "raw materials" for biologic treatments, and because safety of living donors is a related and important public health issue in itself.

Biovigilance incorporates a program to maximize the safety of blood, organs, and HCT/Ps. Some experts have framed the basic elements of biovigilance as

consisting of adverse event monitoring (for recipients and donors), product quality assurance (including processing controls and error management), emerging threat assessment using epidemiologic and laboratory data (e.g., bioinformatics, repositories), and measurement of availability and appropriateness of use. There are two main types of approaches to these issues, one utilizing data analysis to uncover trends in aggregate data to reveal new concerns or the efficacy of interventions in traditional surveillance, and the other utilizing a "sentinel" approach that quickly detects singular events that pose potential public health threats.

2.4 Surveillance: Sentinel Event Reporting vs. Adjusted Rate Benchmarking

The World Health Organization (WHO) guideline on adverse event reporting emphasizes that the effectiveness of surveillance systems should be measured not only by data reporting and analysis but also by the use of such systems to improve patient safety through active response to data generated (1).

In examining frameworks for implementation of biovigilance systems, including the use of such systems for quality improvement, one must consider what type of event is the target of capture. For instance, in order to capture rare events that are of significant singular importance for patient safety, a sentinel system should be 1) extremely sensitive, perhaps at the expense of specificity, 2) operated in real time in order to allow immediate registry of events, and 3) configured so that communication about the event allows critical response actions to take place.

An effective biovigilance program should be operationally capable of providing the core tools, infrastructure, and logistics necessary to support timely communication of critical information to the right people in order to make essential real-time interventions to avert clinical catastrophe.

On the other hand, surveillance of more common events of interest may be more comprehensive. Capture of more common events also may allow benchmarking through comparison of event rates between facilities, which are most helpful if they are adjusted for factors that are not the focus of comparison. Such risk-adjusted rates allow valid comparisons and analysis, so that a quality program can be implemented and continuously evaluated, either before, during, or after an intervention takes place.

3.0 GLOBAL MODELS OF COMPREHENSIVE HEMOVIGILANCE

Hemovigilance systems arose as a response to the threat of emerging infections to the safety of the blood supply. The recognition of the Acquired Immunodeficiency Syndrome (AIDS) epidemic, which resulted in the deaths of thousands of recipients of blood and plasma products worldwide, led to public debates, commissions of inquiry, and legal prosecution stemming from management of the nascent HIV risk of the 1980s. The epidemic also provided additional stimulus to assess the safety of transfusion services through ongoing risk assessment measures. Hemovigilance was developed first by France in 1993 and featured mandatory reporting; the United Kingdom (UK) developed the first voluntary system in 1996. The European hemovigilance efforts were empowered with the European Blood Directive 2002/98/EC (2).

Subsequently, global solutions to the challenge of hemovigilance represent a spectrum of responses including national blood policies, governance models, and reporting systems that are either mandatory or voluntary. Most developed and developing countries have a national blood policy and a national blood system for collecting blood and making it available to hospital transfusion services. These nationalized structures facilitate the establishment of hemovigilance efforts.

Countries that have developed hemovigilance programs have created and implemented systems as a hybrid of mandatory and voluntary approaches (Table 1), operating under a variety of governance models (Figure 1). Hemovigilance systems, depending on the country, are governed either by regulators (e.g., France, Germany, Switzerland), blood manufacturers (e.g., Japan, Singapore, South Africa), medical societies (e.g., Netherlands, UK), or public health authorities including regulators (e.g., Canada). Figure 1 is a graphic representation of these programs. Some of these reside within, and derive reporting mandates from, a national ministry of health (3, 4) while others are primarily organized through professional societies or the country's blood collection system with sharing of data to all concerned parties (2, 5, 6, 7, 8). The European Union currently requires implementation of a hemovigilance system in each member state with reporting to a central office (9, 10, 11).

Outside the European Union, the more recently formed Canadian system is of particular interest as an example of a public health-driven model with data flow to the public health regulators. Within Canada, Héma-Québec, a non-profit organization that manages the blood supply for the Canadian province of Québec has placed Transfusion Safety Officers (TSO) within each medical facility. Surveillance in Québec is more active and comprehensive with the

TSO concept in place and perhaps due to this unique characteristic, Québec has a high rate of transfusion adverse event reporting (4). Although each of the existing hemovigilance systems has characteristics unique to the country's own healthcare and transfusion systems, the systems bear multiple similarities and have yielded similar benefits.

With the implementation of hemovigilance systems in Europe, it became apparent that individual countries were using different definitions for events and incidents and there was a wide diversity in methods and systems of reporting. This led to the establishment of the European Haemovigilance Network (EHN) in 1998 with the goal of developing uniform standards and definitions (12).

Table 1. Comparison of adverse reporting requirement of countries represented in the European Haemovigilance Network (EHN)

Country	**Reporting Requirement**	**Haemovigilance Reporting to Ministry of Health or Regulator**
Austria	Unable to determine	Yes, but some SAEs reported in annual report
Belgium	Voluntary	Yes
Croatia	Voluntary	Unable to determine
Denmark	Voluntary	No
Finland	Mandatory	Yes
France	Mandatory	Yes
Greece	Voluntary	Unable to determine
Iceland	Voluntary	No
Ireland	Voluntary	Irish Blood Transfusion Service
Italy	Unable to determine	Unable to determine
Luxembourg	Mandatory	Report is to blood service of Red Cross but MOH is also notified
Malta	Unable to determine	Unable to determine
Netherlands	Voluntary	No
Norway	Unable to determine	Unable to determine
Portugal	Voluntary	No
Slovenia	Unable to determine	Unable to determine
Sweden	Unable to determine	Unable to determine
Spain	Unable to determine	Unable to determine
UK	Voluntary	Reported through SHOT

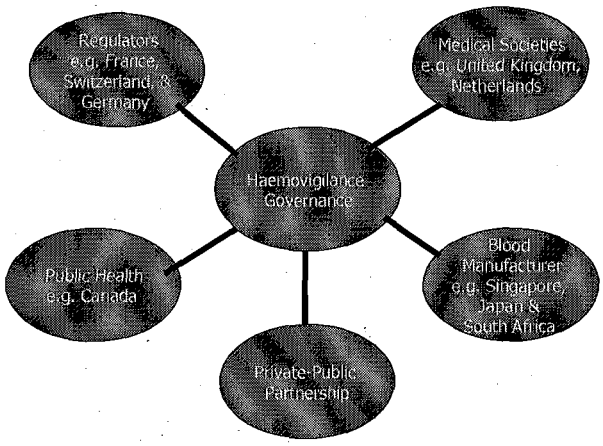

Figure 1. Governance models of various hemovigilance systems in various countries

The EHN defines haemovigilance as a set of surveillance procedures covering the entire transfusion chain (from the donation of blood and its components to the follow-up of recipients of transfusions), intended to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products, and to prevent the occurrence or recurrence of such incidents (2).

The European blood directive 2002/98/EC established the definitions for Haemovigilance, Serious Adverse Events and Serious Adverse Reactions (13). The EHN initially defined grading for severity, imputability and clinical and biological signs (9), which have been modified and expanded by the International Society for Blood Transfusion (ISBT) Working Party. Nevertheless, variability still exists in some definitions, terminology, standardized reporting, etc. Also, the scope of various countries' systems is varied. For example, the UK's Serious Hazards of Transfusion (SHOT) focuses only on serious hazards and does not report mild febrile or urticarial reactions and since most non-hemolytic transfusion reactions show mild signs, reports from SHOT demonstrate a very low incidence of overall adverse events compared to France (14). Others have published the value of reporting near misses (15, 16). The differences from country to country have been recently reviewed (6).

Since the founding of the EHN, the network has expanded to include countries outside of Europe including Canada, New Zealand and Singapore. In addition, the International Society for Blood Transfusion (ISBT) has played a leading role in standardization. Working parties were created in 2002 within ISBT to establish definitions in order to make data comparable between members. There are more than 50 members from 34 countries represented in the EHN. Recently, EHN changed its name to the International Haemovigilance Network (IHN).

4.0 HEMOVIGILANCE EFFORTS IN THE UNITED STATES: A PATCHWORK OF BLOOD SAFETY PROGRAMS

4.1 Blood Recipients and Transfusion-Related Adverse Events

4.1.1 Federal Government Activities

Although national hemovigilance systems are well established in most developed countries, in the US, there is no single program of centralized blood safety monitoring. Ensuring the safety of the US blood supply is a public health responsibility designated to the Assistant Secretary for Health (ASH) as the Nations Blood Safety Officer. Coordinated safety and public health efforts are shared among operating divisions of HHS, including the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), National Institutes for Health (NIH), and Centers for Medicare and Medicaid Services (CMS) (17). Together, these HHS agencies identify and respond to potential threats to blood safety, develop safety and technical standards, monitor blood supplies and help industry provide an adequate supply of blood and blood products. However, by their design, the existing systems focus primarily on reporting of sentinel events. The existing systems do not provide comprehensive baseline surveillance reporting of known events in relation to blood product exposures. Thus, in the US, currently it is not possible to routinely monitor adverse event rates outside of limited, specially designed studies.

The FDA has regulatory responsibility for blood and blood products, and takes on most of the work of risk management. In the US, blood and plasma is collected, processed and distributed by a private industry that is regulated by the FDA primarily under the authority of two national laws. The Public Health Service Act (PHS Act) (42 USC 201 [check] et. seq.) has two relevant sections. Section 351 sets forth the authority for licensure and regulation of biological products while Section 361 defines authorities for communicable disease control. The second national law is the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 USC 201 et. seq.), which provides authority for the regulation of medical products, including drugs and medical devices. Biological products fall within the scope of the FD&C Act because they also are drugs or medical devices. In September 2007, Congress passed the Food and Drug Administration Amendments Act of 2007 [FDAAA]), giving the FDA additional authorities over FDA-regulated products, including biological products. Blood collection and transfusion organizations also comply with State laws and voluntary standards developed by stakeholder organizations such as the AABB (formerly the American Association of Blood Banks) and the PPTA (Plasma Protein Therapeutics Association). Interstate distribution of biological products (including distribution outside of the US) is only

permissible under FDA license. There are approximately 1090 FDA-licensed blood collection establishments and 374 FDA-licensed plasma collection establishments. Approximately 770 unlicensed, but registered whole blood facilities collect and manufacture blood components for intrastate distribution. Within FDA, the Center for Biologics Evaluation and Research (CBER) regulates the collection of blood and blood components used for transfusion. CBER also regulates blood products derived from blood and blood components, such as clotting factors, and CBER establishes reference standards for many of the products. CBER also regulates related products such as cell separation devices, blood collection containers and HIV and other infectious disease screening tests that are used to prepare blood products or to ensure the safety of the blood supply. CBER develops and enforces quality standards, inspects blood establishments prior to licensure of new products, and monitors mandatory and voluntary reports of errors, accidents and adverse clinical events. Post-market inspections of blood establishments are conducted by the FDA Office of Regulatory Affairs, in conjunction with the CBER Office of Compliance and Biologics Quality (OCBQ) and other FDA Offices, including the Office of Blood Research and Review (OBRR).

In 2006, CBER formed the Blood Safety Team (BST) with membership from several CBER offices. The BST's goals are to improve the FDA responses to blood safety issues through defined interoffice collaboration within CBER; to create increased sensitivity to safety signals; to improve the value of safety information; to establish roles and responsibilities in the management of blood safety issues; to broaden public and regulated industry access to the information; to improve the processing of blood safety information through establishment of a forum for review and evaluation of events; and to enhance external outreach, evaluation and risk communication. Although activities of the BST promote effective interagency cooperation, BST participation does not extend outside FDA.

Regulatory oversight of hospital transfusion services occurs through CMS or accredited organizations granted deemed status under the Clinical Laboratory Improvement Amendment of 1988 (CLIA). Although transfusion services are subject to applicable FDA regulations, they are not required to register with FDA unless they also manufacture blood or blood components and they are not routinely inspected by FDA. However, hospital transfusion service laboratories are required to be certified by the CLIA program, and they are routinely surveyed for CLIA compliance. These surveys are addressed in a Memorandum of Understanding between CMS and FDA. CLIA regulations require laboratories to report transfusion fatalities to FDA, and CMS and FDA routinely cooperate in the investigation of these fatalities. CLIA regulations directly reference certain FDA regulations that apply to transfusion services.

In 1997, the FDA initiated the Blood Action Plan to increase the effectiveness of its scientific and regulatory actions, and to ensure greater coordination within PHS. The Action Plan addressed focused areas of concern such as emergency operations, response to emerging infections, and updating of regulations. The plan was adopted by HHS as a whole and progress has been remarkable with many outcomes (Appendix 1)

In 2005, the ACBSA made recommendations on the development of a strategic plan for the blood system as a follow-up to the 1998 Blood Action Plan. A key element of the ACBSA recommendations was development of a biovigilance system. In October 2008, elements of the ACBSA recommendations were incorporated into the Secretary's Office of Public Health and Science strategic plan (Appendix 2).

Reporting to FDA is required for blood and blood components when a fatal adverse event occurs related to donation or transfusion (18). Based on data collected in 2008, the top five leading transfusion related fatality categories were transfusion related acute lung injury TRALI (35%); ABO blood group hemolytic transfusion reactions (22%); non-ABO hemolytic transfusion reaction (15%); microbial infection (15%) and transfusion associated circulatory volume overload (TACO) (7%). Collection of information from the currently required FDA fatality reports for disorders such as TRALI have led to increased understanding of the possible role of plasma and anti-HLA and anti-leukocyte antibodies in TRALI pathogenesis.

In addition, there is a requirement for licensed and registered blood establishments and transfusion services to file biological product deviation reports (BPDRs) when a deviation from standards, such as a variation in current Good Manufacturing Practice (cGMP), may affect the safety, purity or potency of a blood product and the unit leaves the facility's or a contracted facility's control before the problem is identified and rectified. For non-fatal adverse events, blood collection and transfusion facilities are required to conduct investigations and maintain records and reporting to FDA is encouraged, but not required, and is uncommon.

Medical device manufacturers must submit adverse event (AE) reports to FDA involving deaths and serious injuries or illnesses connected with the use of medical devices used for the collection or administration of blood components for patient treatment or diagnosis.

For voluntary reporting related to any FDA-regulated product, patients, family members, physicians, pharmacists and any other reporter can submit information to FDA's Adverse Event Reporting System (AERS)/MedWatch

(19). This system gathers information on a variety of products including drugs, devices and other medical and nutritional products.

CDC's mission is to collaborate with state and local health departments to create the expertise, information, and tools needed to protect public health through health promotion, disease prevention, and preparedness for new health threats. Areas of focus concerning blood, organ, and tissue safety at CDC include public health investigation, surveillance, research, prevention, and risk communication. A stated CDC goal objective is to improve surveillance for adverse events associated with use of biologic products (e.g., blood, organs, and tissues), vaccines, drugs, or devices by coordinating HHS efforts to enhance rapid detection and implementation of novel prevention. Proposed measures and actions include implementation of transfusion and transplant adverse event surveillance. One CDC system for healthcare-related event surveillance is the National Healthcare Safety Network (NHSN). NHSN is a secure, internet-based surveillance system that collects data from voluntarily participating healthcare facilities in the United States to permit benchmarking of adverse events, including healthcare-associated infections, among patients and healthcare personnel.

CDC has had in place since 1998 a blood safety monitoring system in the bleeding disorder community, the Universal Data Collection program, managed by the Division of Blood Disorders, that provides annual testing for hepatitis and HIV and stores blood specimens in a serum bank for use in future blood safety investigations [MMWR 2003]. CDC works with local state health departments to investigate any seroconversions to rule out transmission from blood products used to treat hemophilia and other bleeding disorders. A similar system has been established in several centers in the U.S. that treat patients with thalassemia who depend on frequent blood transfusions for survival. Currently there are over 70,000 plasma specimens on patients with bleeding disorders (primarily hemophilia) and about 1,000 specimens on patients with thalassemia in the CDC bleeding disorder repository.

The Office of Blood, Organ, and Other Tissue Safety operates within the Division of Healthcare Quality Prevention in the Coordinating Center for Infectious Diseases. The Office functions are to coordinate CDC activities to prevent disease transmission and other adverse events; develop, implement, and evaluate CDC's agenda for blood safety; direct CDC representation on standing HHS and industry committees to determine blood safety policy; and chair the Blood, Organ, and Other Tissue Safety Working Group.

The Blood, Organ, and Other Tissue Safety Working Group is composed of division representatives of the Coordinating Center for Infectious Diseases

and liaison members from other areas of CDC, including the Division of Blood Disorders. Functions are analogous to the BST at FDA/CBER to enhance investigation coordination. In addition, the working group coordinates current and planned projects; identifies gaps and priorities for intervention; and develops an agenda to enhance transfusion and transplant safety, in collaboration with HHS and external partners.

The National, Heart, Lung, and Blood Institute (NHLBI) of NIH is responsible for funding basic, translational, and clinical research related to transfusion. NHLBI funds biospecimen collections (Table 2). A vast majority of these collections are maintained at the NHLBI Biologic Specimen Repository. Research is also conducted by intramural FDA, CDC, and NIH scientists.

Within the Office of the Secretary of HHS, the ASH has been designated as the Nation's Blood Safety Officer. This role was established as an outcome of an internal review of the Institute of Medicine's report in the mid 1990s. The ASH carefully considers public discussion of issues and recommendations from the ACBSA. In addition, the ASH participates in internal discussions with the Blood Safety Council (BSC), which often provides input and recommendations on blood policy matters. The BSC consists of senior executive representatives from FDA, NIH, CDC, HRSA, and CMS. The BSC's role is currently being reviewed and a new charter has been proposed to expand the BSC'oversight to organs and tissues. Monitoring of the blood supply and demand is obtained through voluntary reporting through the Blood Availability and Safety Information System (BASIS).

Table 2. Donor, recipient, and linked donor-recipient repositories in the US.					
Name of study*	Timeframe of funding	Sample population	Sample type	Number of samples	Major agents studied
NIH-Clinical Center	1968-97	Donor-Recipient	Serum	29,055 donations 3,429 recipients	HCV, HGV/GBV-C, TTV, SENV
TTVS	1974-79	Donor-Recipient	Serum	5,655 donations 1,533 recipients	HCV, HBV, HHV-8
TSS	1984-85	Donations	Serum	201,212 donations	HIV, HTLV
FACTS	1985-91	Recipients	Serum	11,494 recipients	HIV, HTLV, HCV, HHV-8, T. cruzi
REDS GSR/GLPR	1991-94	Donations	Serum (GSR) Plasma; frozen whole blood (GLPR)	508,151 donations (GSR) 147,915 donations (GLPR)	HBV, CMV, HHV-8
VATS	1995-99	Donor-Recipient	Plasma; frozen whole blood	3,864 donations 531 recipients	HIV, CMV, HBV, HCV, HGV, HTLV
REDS RADAR	1999-2003	Donor-recipient	Plasma; frozen whole blood	13,201 donations 3,574 recipients	Parvovirus B19
TRIPS	2001-ongoing	Donor-recipient	Plasma; frozen whole blood	4,401 donations 879 recipients	HIV, HBV, HCV, HHV-8, CMV, EBV, Parvovirus B19

* All the collections in the table are housed at the NHLBI Biologic Specimen Repository except the NIH-Clinical Center and the FACTS repositories which are retained by the primary investigators.

4.1.2 Public/Private and Private Sector Activities

Unlike the national blood systems that are in place through much of the developed world, the US blood and plasma supply is collected by privately owned and operated facilities that are regulated by FDA. Whole blood for interstate distribution is collected by 135 not-for-profit FDA-licensed blood establishments operating 1,090 fixed community blood collection centers. It is estimated that the American Red Cross (ARC) collects approximately 42% of the US red blood cell (RBC) supply through its network of 35 regional blood centers and operates under a single FDA license. An additional 52% of the RBC supply is estimated to be collected by 77 independently licensed blood establishments that are members of America's Blood Centers (ABC). The remaining 6% of the RBC supply is collected by hospitals (approximately 5%), and the Department of Defense (1%). Blood for intrastate use only is collected by 710 hospitals and other entities that are not licensed, but are registered with and inspected by the FDA and must follow all applicable laws and regulations. Source Plasma is collected in the US by 57 licensed establishments at 373 collection facilities.

The professional organization, the independent blood collectors association and the ARC have also engaged in gathering safety data for assessing risks. The professional organization is represented by the AABB, of which nearly all blood collection establishments and most transfusion services are members; while the ABC represents collaboration among independent, community-based blood programs.

HHS sponsors the National Blood Collection and Utilization Survey (NBCUS) through competitive contract to assess the amount of blood collected and transfused, and hospital activities involving tissues and cellular therapies in the US. The facilities surveyed include all non-hospital-based blood collection centers, a statistically representative sample of hospitals from the American Hospital Association (AHA) database and a similar sampling of cord blood banks. The data obtained by this survey are vital in determining estimated numbers of collections and transfusions as well as trending of utilization. Some data on adverse events, defined as numbers of events that require diagnostic or therapeutic intervention, are also collected (20). The national data are helpful in determining the denominator for comparison of activities and events.

Blood collection centers also operate their own reporting systems. ABC, through its alliance of independent blood centers, conducts a variety of surveys among its members on a periodic basis and shares outcomes and best practices through online reports to its participating members. Some members of ABC are blood collection centers that also function as transfusion services

and collect and monitor adverse reactions in a fashion similar to hospital based transfusion services (21). These activities however are for internal use and quality control and are, in general, not shared publicly. Individual blood centers are also required by FDA to document errors and adverse events, perform investigations, document corrective action when warranted, and report to FDA any biologic product deviations that are present in products that are made available for release from the manufacturing facility.
The 35 ARC regional blood centers actively solicit reports of infectious and noninfectious complications in recipients of blood components. When transfusion reactions are reported within ARC, investigations are performed locally and then by region. Regional medical directors evaluate the investigations and assign probability scores. Outcomes are compiled and entered into the Donor and Recipient Complications Program (DRCP) database. This provides the ability to track and analyze trends in complications at each region and across the ARC system to provide opportunities for process improvement. Specific outcomes are also published periodically through peer-reviewed journals (22).

Mandatory reporting requirements from some state health departments also exist. For example, since 1989, the New York State Department of Health has required the reporting of all transfusion-associated incidents in the state that pose a significant risk to the donor or to the recipient, whether or not an incident results in an adverse outcome (23). Approximately 250 New York hospitals use action and root-cause analysis results and delineation of corrective actions taken. Compliance is verified during biennial inspections. For transfusion-related events, reports are assessed for completeness, and missing information is sought. The observed rate of giving incorrect ABO blood group and type is reported to be 1/19,000 transfusions. This rate is very similar to the 1/18,000 reported by SHOT; however the true error rate may be much higher.

In 1996, The Joint Commission (TJC, formerly the Joint Commission on Accreditation of Healthcare Organizations) an organization responsible for accreditation of healthcare facilities in the US, established a sentinel event reporting system in support of its mission to continuously improve the safety and quality of health care (24). TJC reviews organizational responses to sentinel events as a part of its accreditation process. Sentinel events are defined as an unexpected occurrence involving death or serious physical or psychological injury, or the risk thereof. Serious injury specifically includes loss of limb or function. The phrase "or the risk thereof" includes any process variation for which a recurrence would carry a significant chance of a serious adverse outcome. The Sentinel Event Policy requests the organization to transmit its root cause analysis, action plan, and other sentinel event-related information to TJC electronically (25). Transfusion errors, primarily

misidentification of patient or product, are expected to be reported as sentinel events should they lead to severe harm.

4.1.3 US Transfusion Hemovigilance Initiatives to Date

While there is no formal hemovigilance program in the US, mandatory and voluntary reporting requirements exist within healthcare facilities. For example, most hospitals have a transfusion reaction reporting system that reports to the hospital transfusion service. A transfusion committee made up of various department representatives (26, 27) may review the reports or in some facilities this may be an additional responsibility of the Pharmaceutical and Therapeutic Committee. This control at the local level is important since it offers the opportunity for a uniformity of practice at the hospital level, including common definitions, and implementation of corrective actions when system problems are identified within a specific facility or hospital system (17, 28). However, benchmarking to external institutions is lacking in this model. The French experience has demonstrated the benefits of comparison to other hospitals for participation in a national hemovigilance program (29, 30).

Prototypes have also been created to detect transfusion errors. The Medical Event Reporting System for Transfusion Medicine (MERS-TM) was developed under the leadership of Columbia University, New York, with funding from NHLBI to collect, classify and analyze events that could compromise the safety of transfused blood and to facilitate system improvement (31). MERS-TM defines a medical event as any error, incident, deviation, variance, or sentinel/adverse event related to blood components and transfusion procedures. An avoidance or prevention of an unwanted consequence through some action that identified and corrected the potential failure is considered a near miss.

The MERS-TM system was designed to function within existing quality assurance programs using descriptive classification schemes and FDA coding. The system was tested within blood centers and transfusion services. Currently functioning, this small system provides mechanisms for approximately 20 hospitals to submit reports anonymously to a central database, which supports analysis of an individual hospital's data as well as comparisons to that of the aggregate data (32, 33). This approach has demonstrated that, for the facilities participating, 90% of reported events are near misses of which 10% were detected after product issue, but before transfusion.

4.2 Gaps in Current US Transfusion Recipient Adverse Reaction Reporting Systems

Gap 1: Patchwork and sometimes fragmented system of various adverse event reporting

The responsibility of hemovigilance, and more broadly biovigilance, within the federal sector has been divided by HHS agencies based on their specific mission and regulatory authority. There is currently no comprehensive HHS system to share data among the HHS operating divisions, or externally.

The US blood collection and transfusion system is comprised of a network of private sector blood establishments and hospitals that maintain strong affiliations with accreditation and trade organizations. Adverse event reporting is conducted within individual facilities and sometimes shared within the larger organizations, but lacks uniformity of definitions, procedures, and assessments. There is also limited information exchange between stakeholders. In many cases, data are considered proprietary until they are published in the scientific literature.

Gap 2: Likely under-reporting of transfusion adverse events

Despite reporting requirements and an existing patchwork of systems, there are many challenges in effectively detecting transfusion reactions in recipients. First, separating complications of transfusion in recipients from conditions due to the underlying illnesses that prompted the need for transfusion is difficult. The development of computerized health services data could improve the quality and availability of recipient data. This type of initiative would require significant investment in infrastructure. Evaluation of international systems (such as SHOT in the UK) and standards could prove useful in identifying possible modifications and improvements to the US system.

It is likely that there is under reporting to FDA, even for required adverse events (i.e., fatality reporting for blood and blood components)). This under reporting ("numerator" deficiencies) has been attributed to a number of factors, including uncertainty about the relationship of the fatality to a transfusion event, the time and effort required for filing a report, or concern by a potential reporter about resulting regulatory actions. As an example, TRALI remains the most frequent cause of US fatalities following transfusion with 34 cases reported to FDA in 2007 for a reported rate of 1.2 TRALI cases per million transfusions (all components)(34). This is a substantially lower rate than reported by SHOT prior to the institution of male only plasma (35).

According to the 2005 NBCUS Report, there were 32,128 medically significant transfusion-related adverse reactions in 2004. After adjusting for the survey response rate, one can estimate that there are over 50,000 significant transfusion reactions per year in the US, many of which are preventable. The 2007 NBCUS report registered 71,994 transfusion reactions in 2006 for an overall reaction rate of 1:320 transfusions for all components (36). This is about one half of the 1:150 rate overall reported by the active hemovigilance system in Québec, Canada (7). Extrapolation of the Québec estimates would translate into nearly 120,000 adverse events in the US based on 2004 red cell utilization data (20). Including other blood components would significantly increase that number.

Finally, increased knowledge about the potential risks of transfusion to recipients could lead to more careful assessment of the need for transfusion of blood and blood components and reduction in the number of transfusions that do not meet accepted practices.

Gap 3: Challenges with FDA-required reporting

Current FDA regulations 21 CFR 606.170 require that blood collection or transfusion establishments investigate adverse reactions resulting from blood collection or transfusion. The establishments must investigate these adverse reactions and maintain records of their investigation at their facility. If it were determined that the blood caused the transfusion reaction, then the report must be forwarded to the blood collection facility. Currently, blood establishments are not required to submit these reports to FDA, although FDA can review these reports on inspection. FDA has proposed reporting requirement for serious adverse events related to blood collection and transfusion, in the proposed Safety Reporting Rule (SRR), published on March 14, 2003 in the Federal Register. (http://frwebgate5.access.gpo.gov/cgi-bin/waisgate.cgi?WAISdocID=906650192596+0+3+0&WAISaction=retrieve). FDA currently is considering the comments received and a timeline for final publication of this rule is not currently available.

Important trends in the data submitted under regulatory requirements may not always be identified or understood because of the limitations placed upon data that are reported to the federal government. Biologic Product Deviation Reports (BPDRs) required by 21 Code of Federal Regulations (CFR) 600.14 and 21 CFR 606.171 are examples. There is a need to develop more sophisticated analyses of the data collected BPDR reports, but this ability is hampered by the lack of more detailed characterizations of reported product deviations within the reports themselves. More detailed analyses would better define underlying reasons for deviations, provide useful benchmarks, and provide additional incentives for changes in practices in blood

establishments and transfusion services. As a hallmark of the future, electronic reporting for BPDRs has significantly reduced the paperwork burden for both regulated industry and the FDA associated with reporting, receipt, and analysis of BPDR reports. Arguably, the burden of BPDR reporting is in need of examination to focus reporting and analytic efforts on the manufacturing deviations that have the highest predictive value to identify unsafe units and then share this information proactively to help improve quality control and quality assurance efforts at the manufacturing level. FDA is actively reviewing certain categories of post donation information (PDI) and has recently removed the requirement for reporting donor history of cancer.

It should be noted that FDA-required serious adverse event reporting will not provide for the collection of incidents related to less serious events, or near-misses that can detect safety signals for further investigation. These are important signals that are effectively captured by more broadly-based hemovigilance systems.

A Sentinel Initiative, recommended by the 2006 Institute of Medicine Report, currently under early development in the FDA Office of Critical Path Initiatives will establish data mining capability across HHS (e.g. CMS) and non-government sites (e.g. pharmaceutical manufacturers) and aims to develop a national, electronic network to link data on 100 million patients from multiple existing health care data systems by 2012 in order to conduct post-licensure safety monitoring of FDA-regulated medical products. Blood products, particularly plasma derivatives dispensed by pharmacies, as well as blood-related devices will be studied in the same fashion as drugs, vaccines, and other medical products. (See, for example, the extensive research methods and record of the CDC Vaccine Safety Datalink at http://www.cdc.gov/vaccinesafety/vsd/). In addition to facilitating pharmacoepidemiologic safety signal searching, safety hypothesis refinement, and safety hypothesis testing studies, the systematic study of special hazards of blood and blood products will likely become much more efficient because a range of information resources at participating sites will be potentially accessible. As one example, acute hemolytic transfusion reactions can follow mistakes in matching products to patients. These human errors might be possible to track by time of day, day of week, and other variables that could point to opportunities for development of additional preventive methods. ICD-9 and ICD-10 discharge diagnoses are often useful in finding patients who have particular diseases, and then blood bank, pharmacy, and other linked records can clarify when some of these "case patients" had been exposed to medical products that might have contributed to their illness. Patients with babesiosis can be identified, for example, and then their prior transfusion history will be available for analyses.

Additional information about the Sentinel Initiative is available at these sites: http://www.fda.gov/oc/initiatives/advance/reports/report0508.html

http://www.fda.gov/oc/initiatives/advance/sentinel/factsheet.html

Gap 4: Need for accurate recipient denominator data, precise definitions, and training

The potential pitfalls of any adverse event reporting system include fragmented reporting, incomplete reports, lack of control groups (e.g., those not transfused but with similar adverse events) to establish causal relationships, incomplete or absent denominator information, and a passive and voluntary surveillance system with under-reporting, biases and confounding factors.

For rates to be accurately calculated there is a need to determine the precise number of units of blood and blood components produced and distributed by blood establishments and transfusion services in the US as a "denominator". With this information, adverse reaction reports, BPDRs, fatality reports, and safety signals can be put into perspective on a national, regional, and local level. The availability of a denominator facilitates the interpretation of reports and the evaluation of potential sentinel events. Potentially, data could be obtained from hospital outpatient services or from CMS records if diagnostic-related group (DRGs) were revised to capture use of blood and blood components as a separate category. BASIS provides nationally representative current usage information. BASIS could also be used to survey specific safety issues through targeted initial data collection from participants. Mathematical modeling can be developed and used to predict blood use and availability, an indirect measure of the denominator.

Whether dealing with clinical events, such as transfusion reactions, or near-miss incidents, a clear and precise set of definitions is lacking throughout the US. The recent experience with the utilization of definitions recommended by a 2004 Canadian Consensus Conference for TRALI (37) is a case in point. An AABB survey carried out 2 years later demonstrated a wide variability in procedures and policies related to the diagnosis, donor investigation and/or management of TRALI cases (38). The working party of ISBT has developed definitions of transfusion reactions that could be used to achieve commonality and facilitate meaningful comparisons of data between countries.

The multiplicity of laboratory information systems can also be an impediment in implementation of a comprehensive national framework. To be successful, in addition to the issues mentioned above, simplicity and ease of use are important elements. Building interfaces to existing reporting systems need to

be considered from the beginning. Optimally, a national hemovigilance system would be interfaced to a facility's internal error management software (such as MERS-TM) and be able to accept the report of the necessary elements of a case automatically. Most hemovigilance systems have not reached this level of sophistication.

Finally, healthcare providers need more awareness of transfusion adverse events. For any reporting system to be reliable, those charged with capturing the event must be cognizant of the commonly recognized signs and symptoms of transfusion reactions as well as unusual events during or after a transfusion. Unfortunately, those responsible for transfusion are not always adequately trained to recognize such events, and provider education and practices vary from hospital to hospital.

As mentioned before, Canada, particularly Québec, has moved forward with TSOs, but other countries, including those in Europe, are wrestling with the concept of hiring TSOs in every hospital due to cost constraints. The appointment of at least some personnel associated with quality assurance to be tasked with transfusion outcomes would greatly improve education and process improvement at the transfusion facility.

In summary, gaps in the current system can be addressed by improving reporting compliance, enhancing oversight though increased reporting requirements, improving data analysis, improving data feedback and education, and creating standardization within and between interfaces at the facility level.

Gap 5: No national surveillance of donor serious adverse events other than fatalities

Overall surveillance of donor serious adverse events other than fatalities is not conducted systematically in the US. However, several large efforts to collect donor adverse event data have been initiated among major blood collection organizations.

Most blood centers collect data on reactions of various types but there is no universally accepted set of definitions for comparative purposes. ISBT lists 25 categories of events, ARC has 15 and ABC has 9. A primary charge to the AABB donor biovigilance working group is to harmonize these definitions if possible. As previously mentioned, individual center data reports have been useful in focusing on particular areas of concern but no national database, or even standard definitions, exist.

Donor events are particularly complicated in precisely defining the focus of adverse events of interest. One can examine 1) adverse reaction occurring from donation, 2) donor screening markers, or 3) post-donation outcomes. Data on adverse events in blood donors have not been included in national hemovigilance systems until recently and are thus not as well developed as recipient adverse event reporting. Studies have been reported from single centers in the US (39-42) and in Europe (43), and comprehensive national data have been reported from France and Denmark (44, 45). In 2004, a joint working group from the ISBT and EHN was established, and has proposed a classification and a set of definitions of complications related to blood donation to form the basis for a registry.

Regulatory oversight of donors includes determination of donor eligibility and extends to protections of donor health and safety. Donation-related fatalities must be reported to FDA (21CFR606.170 (b)) within seven days after a thorough investigation (21CFR606.170 (a)). Aspects of this process are clarified in Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion (September, 2003). Data analysis at FDA is largely descriptive and is accomplished through specific follow-up investigations and epidemiologic trending of fatality reports.

In the US, the ARC initiated a comprehensive hemovigilance system in 2003 that includes complications of blood donations (42). The program prospectively monitors donor complications associated with allogeneic whole blood (WB), apheresis platelet (PLT) and automated 2-unit red cell collection (R2) procedures in 35 blood collection regions. All regions follow standard operating procedures including recording all adverse reactions on the blood donation record according to a standardized classification scheme and captured in a central electronic database. There are 15 reaction categories which incorporate a severity rating (minor, major) for reaction types in most categories, and every category is further divided into whether the donor received outside medical care. All major reactions at the time of donation and all reactions that are reported to the blood center after the donor leaves the collection site are captured on a standard case report form, investigated, and reviewed by the blood center physician and reported in a tally on a monthly basis to the National Medical Office which compiles and analyzes data. Complication rates for different procedure types and among different age groups are compared by calculating odds ratios and 95% confidence intervals.

In 2006, the American Red Cross performed a total of 6,014,472 whole blood collections in the US: 209,815 were associated with adverse reactions (349 per 10,000 donations or 3.5%). Minor events (e.g., pre-faint or vasovagal-type) reactions accounted for the majority of reactions (258.3 per 10,000

collections)(42).

The second largest blood collector in the US is Blood Systems, Inc. (BSI) which consists of United Blood Services (UBS), Blood Centers of the Pacific (BCP), Tri-Counties Blood Bank in California, United Blood Services Central Coast California, Community Blood Bank, Rancho Mirage, CA and is affiliated with Inland Northwest which has collections in Washington and Idaho. Operating procedures and software are not the same at UBS and BCP. BSI collected 941,357 whole blood units in 2006. Blood donor reactions are classified as mild, moderate or severe (46). Mild reactions are noted on the donation records. Each center provides information on reactions using a standardized adverse reaction reporting form. These paper records capture incidents related to needle insertion such as bruises and hematomas; and on moderate and severe reactions include descriptions such as time and duration, symptoms, monitoring and management of the reaction. Data is entered into a database for further analysis. BSI reported an overall reaction rate of 1.43% for 2006 which is lower than previous reports (42, 47).

America's Blood Centers (ABC) is a trade organization with members from 77 community-based blood centers around the US and Canada. ABC members collect more than 9 million units of whole blood – half of the US blood supply and all of Canada's volunteer donor blood supply. Recently ABC established a data warehouse initiative, which includes a comprehensive plan for data collection, benchmarking and sharing of best practices. Although the ABC membership is not required to participate in the data warehouse, the initiative is meant to streamline current activities, combine efforts, reduce member and staff workload, and establish a formal policy governing use of surveys and data. The initiative includes design, development, validation, and implementation stages for accumulating, organizing and reporting on the collected data including donor adverse reactions. Local decisions will determine quantity of data entered into the data warehouse. This data collection tool is built so that very detailed information can be collected on each donor reaction, including demographic information on the donor and signs/symptoms. The final phase of the project will be to establish a method to download donor incident data stored either in the Blood Center mainframe computer or in the ABC Donor Reaction Tracker into the ABC Data Warehouse.

Previous efforts to establish reporting on donor events have focused on specific emerging infectious diseases through results of donor testing. This has been limited specifically to WNV and Chagas testing through AABB. The epidemic outbreak of WNV resulted in establishment of a public-private partnership between AABB and several government agencies to collaborate on the response to this emerging public health disease threat. The task force

included representatives from AABB, Department of Defense (DoD), ARC, ABC, Canadian Blood Services (CBS), BSI and HHS operating divisions (CDC and FDA). This AABB Inter-organizational Task Force carried out weekly monitoring of transfusion related cases, prevalence of reactive WNV Nucleic Acid Test (NAT) results and discussions of public health policy including reporting of outcomes (48).

In 2006, an electronic data network for capturing WNV test results from each blood collector was established. The tool was intended to support and enhance the identification and tracking initiative in partnership between HHS and the blood industry when WNV first became a public health concern. The data posted on the AABB Web site is provided by blood collection and testing agencies and provides a unique perspective of the continental distribution of West Nile Virus in blood donors in North America. The WNV Biovigilance Network collates data on donors (blood, tissue and hematopoietic progenitor cells) with suspected WNV infection in the United States and Canada. Data are collected from donor screening tests performed by NAT. The data are reported to the AABB site by facilities responsible for testing virtually all blood donations in the United States and Canada. The reports, provided on a map of North America, illustrate the geographic and temporal distribution of WNV infection as reflected by presumed viremic donors (PVDs) during the peak season (49).

In 2007, a similar effort was established for tracking and mapping of donors screening positive for *Trypanosoma cruzi*, the etiologic agent of Chagas disease. Tracking and mapping of this apparent emerging disease was done in an effort to determine both the prevalence and geographic status of potentially infected donors.

Gap 6: Need for accurate donor denominator data, precise definitions, and training

Even within a single blood system, such as the ARC, with standardized definitions of donor complications and operating procedures, there is considerable variability in reported reaction rates among different regional blood centers. Some of this variability relates to donor demographics including age and differences in rates during the spring and fall compared to summer and winter (50). Nevertheless, ARC has demonstrated that regional variability exists because of the inherent subjectivity in evaluating and recording donor complications. This subjectivity in evaluation and imprecision in coding undoubtedly contributes to regional reporting variability (42).

The limitations of these programs include a lack of systematic collection of data and provide opportunities for future improvements. Many centers focus on moderate and severe reactions, which are the most medically relevant. However, minor reactions can provide important information if rates predict more serious outcomes. Interventions which result in a small reduction in reaction rates locally would require a large dataset to achieve statistical significance, translating into reductions in absolute terms nationally. This, along with identification of rare events, may only be enhanced by a national reporting system with standardized definitions. Furthermore, small blood centers that lack the resources for monitoring any reactions can benefit from practices that establish improved safety measures on a national scale and result in standards setting for the benefit of the donors. Although elimination of all risks to healthy volunteer donors is not possible, reduction in the rate of complications will not only benefit the health and well being of donors but also enhance the likelihood of future donations.

Similar to the need for denominator information about transfusion recipients, donor hemovigilance would benefit from accurate donor denominator numbers, donation frequencies, and broader demographic and other relevant information about the overall pool of donors.

Enhancements in national oversight of those who donate and the donation process could have major benefits, These include: increased donor safety, increased numbers of donors and the resultant size of the blood supply, improved public confidence in the process, and development of devices and software that increase the safety margin for donation. Increased costs associated with enhancements should be balanced by increased public confidence in the donation process and an absolute increase in the number of donors.

Gap 7: Need for accurate tracking of all donor infectious disease test data

Efforts to aggregate blood donor screening markers nationally, beyond WNV and Chagas to include HIV, HBV, and HCV are now underway through collaboration between HHS, AABB's Transfusion Transmitted Diseases Committee (TTD), and the major blood collection centers. At the present time, these data are available but not collected outside of the blood or plasma collection facilities. An attempt was made during the 2007 NCBUS to collect these data, however, methodologies need to be validated (e.g. whether test results should be included in the numerator total results, reactive results, or confirmed test results). It has been proposed to the AABB TTD that a unified national system ideally should track data reflecting whole blood collections, plasma for further manufacture and possibly HCT/Ps. Data for apheresis should also be considered separately due to the unique characteristics of this

critical donor subset and the higher frequency of collections.

Although planning is in place for national coordination, questions remain concerning funding, data ownership and management, maintenance of database and donor elements, and use of the collected data.

Gap 8: Need for timely analysis of reported data

Timeliness of analysis is a major problem with the data currently collected. For example, the NBCUS is conducted every two years but the report may be delayed for publication by up to three years for use by the blood community and the public. Likewise BPDR and MedWatch reports, while collected shortly after an observed event, are summarized and collectively reported, which may result in delays. Information obtained from these data systems could potentially facilitate internal quality audits if analysis of the events and magnitude and incidence of the problems could be reported in a timelier manner.

4.3 Emerging Threat Assessment: Looking Beyond Known Transfusion-Related Events

There is a need to develop informatics and laboratory repository capabilities to meet the challenges presented by emerging infectious diseases (EIDs) and other threats. For example, the NHLBI has sponsored two multi-center Retrovirus Epidemiology Donor Studies (REDS-I and the current REDS-II) that carry out investigator-initiated investigations of transfusion-transmitted viral and non-viral infections, non-infectious complications of transfusion, and other aspects. Several targeted specimen repositories were established by REDS-I, including a matched donor-recipient cell and serum collection (REDS Allogeneic Donor and Recipient - RADAR) that included seven blood centers and eight hospitals. The use of these repositories has been reported in peer-reviewed journals (51). REDS-II has initiated targeted studies of TRALI and other important transfusion-related outcomes.

Rapid worldwide information exchange is also needed to assess the potential impact on means of transmission regarding new or re-emerging agents. Repositories, such as those maintained by funded NHLBI studies and CDC's Universal Data Collection bleeding disorder community repository, may be very useful in defining the onset of human infection with a new EID and learning about its epidemiology and natural history, but vital epidemiologic data must be gathered from global sources before such studies can be put into place. The EID subgroup of the PHS Interagency Working Group for Blood Safety and Availability (i.e., PHS Blood) provides an ongoing platform for information exchange among the PHS agencies; however these efforts need to

be translated into a rapid response plan that will ensure timely protection of the Public Health when an EID appears. More sophisticated real-time informatics methods are needed for timely detection of potential threats to transfusion and transplant recipients.

4.4 A New Initiative: A Public-Private Partnership in Hemovigilance Surveillance Reporting

The national patchwork of reporting systems for blood safety in the US, although providing valuable information, falls short of the advances being made in Europe related to the existence of integrated national reporting systems. As a result, there has been growing interest in development of national programs to improve communication across a variety of reporting systems, collect adverse event and incident data and improve patient and donor safety.

The realization of the shortcomings of the US infrastructure in hemovigilance, as well as the growth and needs of the tissue transplantation field led AABB, in 2006, to incorporate a Biovigilance Network initiative into its strategic plan. This Network is envisioned to enhance cooperation with government and other interested agencies to incorporate transfusion and transplantation (tissue and organ) recipient and blood donor adverse event and incident reporting (27). Due to the multiplicity of both public and private agencies with a stake in such a network, an Inter-organizational Task Force was created to provide representation and input into the process. From this Task Force, a Steering Committee was created with representatives from the private sector AABB, ABC, ARC, BSI and the College of American Pathologists (CAP) and HHS, FDA, NIH and CDC serving in liaison roles from the federal government. The Steering Committee defined the vision, mission/purpose and charges to two working groups representing recipient and donor hemovigilance to provide technical input to allow the development of working surveillance systems in collaboration with the Federal government. The working groups consisted of individuals with expertise in various operational aspects of transfusion services and blood collection. Both groups included corresponding members from the EHN to provide guidance and experience from other systems.

As mentioned as the impetus for this report, also in 2006, the ACBSA recommended that HHS should coordinate Federal government actions and programs to support and facilitate biovigilance in partnership with initiatives in the private sector, including the AABB Interorganizational Task Force on Biovigilance, to advance public health in this effort.

At this time, the opportunity arose to develop a different type of partnership, which recognized the global uniqueness of American healthcare. This partnership marries the benefits of the subject matter expertise available in the private sector with the public health knowledge, ability for data protection, and resource capacity available from the public sector. Hemovigilance is a public health responsibility, but with privacy, confidentiality, and regulatory concerns present on many levels; an independent perspective must be maintained for hospital participation to be maximized.

4.4.1 Public/Private Initiatives in Recipient Hemovigilance

As an example of one product of this collaboration, the AABB and the CDC have entered into a public-private partnership to develop a national hemovigilance infrastructure for transfusion recipient monitoring, as a module of NHSN. Other NHSN modules currently operating include surveillance in over 2,000 hospitals as of May 2009 for the reporting of patient nosocomial infections and healthcare personnel adverse events. The NHSN system overall is a voluntary, confidential, non-punitive third party reporting service. It focuses on improving patient safety and corrective action, is managed by experts with the ability to analyze data and to understand implications for the medical community-at-large both at an early warning/detection level and for long term continuous improvement. There is data access for external analysis, periodic data feedback to participants, and where possible, incorporation into existing systems.

The NHSN hemovigilance system will capture both adverse events (post-transfusion untoward outcomes) and incidents (deviations from standard procedures or other unusual events that did or might have resulted in an adverse event or suboptimal outcome), which will be captured with a simple web portal for rapid manual entry of data. Eventually the system could allow for automatic transfer of data from local systems to the national system. Registration (and annual updates of basic institutional and demographic data) will provide the denominators with which rates of adverse events and incidents can be calculated. The details of these events will be captured through selection from pull-down menus and other simple systems to speed entry. Data will be stored in this secure database that will allow generation of standardized as well as user-defined reports (tabular or graphical) with or without comparative data from the system. Training modules are being prepared to ensure that all can take rapid advantage of the system's capabilities.

The hemovigilance module has been designed to incorporate useful features that have been tested though other systems. The system developed though

the Public Health Agency of Canada has been an excellent model of utility, using the event classification system developed by Dr. Harold Kaplan and colleagues to support the MERS-TM system. The assistance of Canadian representatives on the AABB Working Group has been critical to the rapid development of the US system. The definitions of transfusion reactions that will be used by the network are those developed by the ISBT Working Party on Hemovigilance. As these definitions are being widely adopted around the world, the data generated in the US can be compared with those generated elsewhere, extending the power of the US efforts.

In addition to the participating institutions having access to their own and comparative system data, and compilation of an annual report by CDC on behalf of NHSN participants, a variety of targeted expert analyses and surveillance tracking systems can be utilized. The collection of comprehensive national data for the first time will allow clinicians, researchers and policy makers to view the impact of interventions on the transfusion system both locally and nationally. The system's database design has the capability to evaluate the effect of new interventions, allowing for the exploration of more complex interrelations.

Separately under the guidelines of a Patient Safety Organization (PSO), AABB could query a database derived from consenting NHSN facility participants via the NHSN group function. The PSO goal is to develop recommendations for improved practices to improve transfusion recipient outcome. These analyses would be made available to the PSO membership so that local (i.e., hospital) or regional (i.e., blood center) implementations of improved practices could be designed and undertaken by those closest to the operation as part of their commitment to continual process improvement.

4.4.2 Public/Private Initiatives in Donor Hemovigilance

AABB is also working with HHS in an effort to establish a national donor biovigilance network. Their initial efforts are focused on agreement on definitions of donor adverse reactions including those developed by the ISBT with the objective at arriving at a global set of definitions to facilitate benchmarking around the world.

The greatest impediments to establishing a national system for donor events will be in reaching agreement on definitions and determining how data that are already being collected electronically can be easily transferred to a national database. Even if established, it will be of equal importance that data be captured in such a way that it leads to continuous improvement. Such a system must be easy to use, flexible and responsive to developments in transfusion medicine, and forward looking to justify the expense and effort

in developing and maintaining a national program.

4.4.3 Future Challenges, Including Integration of Private and Public Hemovigilance Efforts

HHS and non-government partners have made substantial progress on national biovigilance collaborations based upon voluntary reporting. This design offers many opportunities for improvements in US national biovigilance capability, including time trending based upon highly refined definitions and imputations, availability of benchmarking data to allow comparative assessment of errors and adverse events at the institutional level, and establishment of national data for comparisons with other hemovigilance systems worldwide.

Any large hemovigilance system faces future challenges, and efforts are underway to address, for example:

1) The precise parameters for sustained public/private shared partnership have yet to be defined. Although there are many opportunities created by a public-private venture, there also need to be clear pathways for long-term governance, including how data is collected, analyzed, and disseminated to improve practice.

2) As part of a national biovigilance effort, the voluntary hemovigilance programs described here must be integrated meaningfully with other systems that are under development, including publicly-funded investigator-initiated research which may offer the most rigorous and efficient design for intervention research.

3) Similarly, biovigilance efforts must also be designed to complement reporting with the proposed FDA Safety Reporting Rule (SRR). Serious adverse events among donors and blood recipients will form a key element of data collection for all of these efforts.

Work has already begun to develop an interface between NHSN facility participants and the FDA MEDWATCH adverse event data collection form, so that at an early stage, anonymous surveillance reports to the NHSN hemovigilance program can be fed to FDA (at the reporter's option) on an identity-linked basis. This will facilitate the identification and investigation of failures related to FDA-regulated products and the identification of sentinel events. As both data collection efforts mature, it is anticipated that the NHSN data collection will increasingly be collected automatically from reporting institutions under HL-7 data standards and that these reports will then form the basis of reporting to FDA through the future MEDWATCH-

PLUS adverse event reporting system (again at the discretion of the reporting institution). While the functionally anonymous system will be optimized for benchmark quality comparisons and trending, the FDA system will permit rapid investigation and intervention based upon observations that may have a time-sensitive impact on public health. Similarly, the existence of FDA-required reporting, implemented through a common data portal, will help to encourage the overall level of reporting.

The current biovigilance patchwork system environment is complex and non-integrated. Since the broadest interpretation of biovigilance represents an umbrella for multiple public and private surveillance and reporting mechanisms, one could imagine a common portal through which systems could be accessed depending on either interest or requirement. As electronic health records (EHR) and information exchange become more widely adopted, electronic exchange of information directly from EHR systems for biovigilance reporting should be integrated (Figures 3-5). It will, in part, be the role of HHS to identify and address these challenges and create a sustainable biovigilance effort of the highest quality to support the public health needs of our donors and blood recipients.

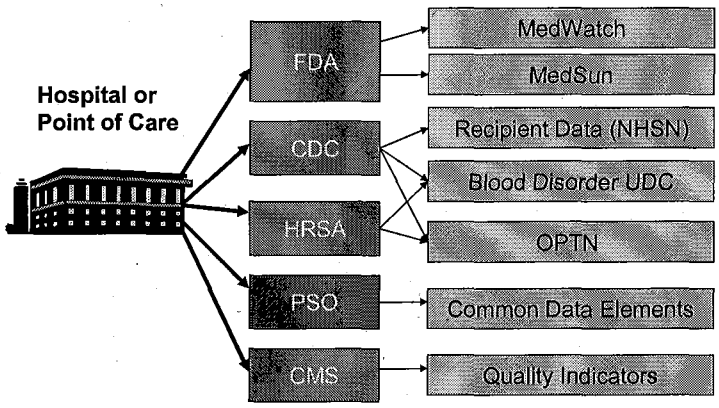

Figure 2. The current patchwork of biovigilance

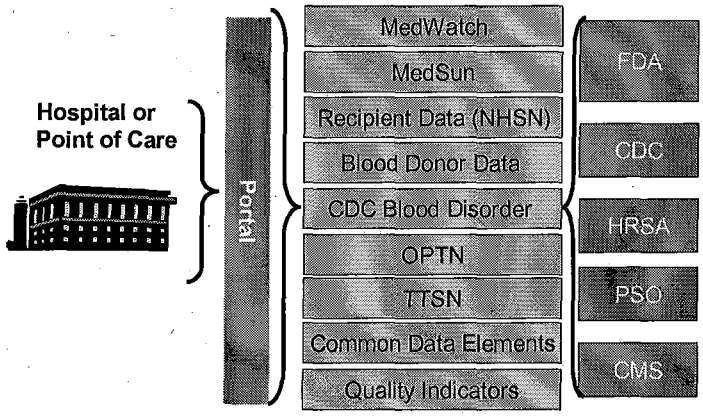

Figure 3. Portal concept of biovigilance reporting

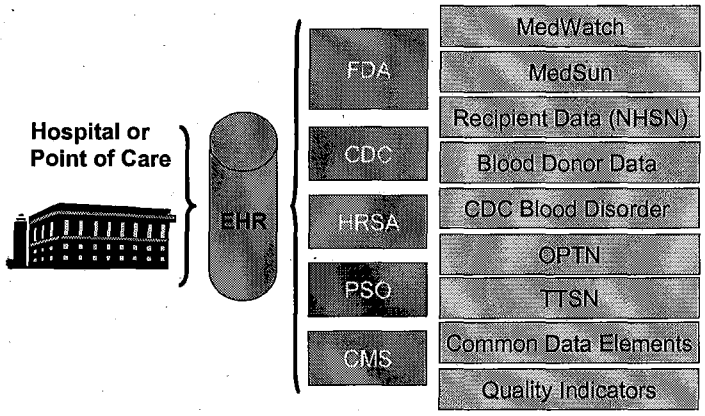

Figure 4. Potential Model of Electronic Health Record (EHR) Exchange Interoperability

5.0 BIOVIGILANCE EFFORTS IN THE US: ADVERSE EVENTS ASSOCIATED WITH HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS

5.1 Background

FDA regulates human cells, tissues, and cellular and tissue-based products (HCT/Ps), defined as articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include bone, ligament, skin, dura mater, heart valves, cornea, tendon, oocytes, semen, and hematopoietic progenitor cells (HPCs) derived from peripheral and umbilical cord blood (UCB). Minimally manipulated bone marrow for homologous use and not combined with a drug or a device is not considered an HCT/P, and is not regulated by FDA. HRSA has oversight of minimally manipulated bone marrow from unrelated donors. This oversight is executed through the Bone Marrow Coordinating Center, a component of the CW Bill Young Cell Transplantation Program, by contract with the National Marrow Donor Program (NMDP). Minimally manipulated bone marrow for homologous use that is not combined with another article and is for autologous or related use is not subject to Federal oversight. For the most part, the collection and infusion of these products occurs in establishments that manufacture HPCs that are subject to oversight. Table 3 summarizes PHS agency responsibility for Federal oversight/regulation of HPCs.

The PHS WG did not perform a gap analysis on reproductive HCT/Ps. Reproductive HCT/Ps have unique issues related to their use, and FDA regulation of reproductive HCT/Ps currently is limited to registration of facilities and listing of products, as well as donor eligibility requirements. The PHS WG also did not include a gap analysis on HCT/Ps subject to pre-market review and licensure by FDA. HCT/Ps subject to licensure must comply with additional regulations; must demonstrate safety and efficacy; and are subject to a comprehensive set of event reporting requirements. Examples of HCT/Ps that are or will be subject to licensure are peripheral blood stem cells (PBSC), UCB from donors unrelated to the recipient, and somatic cellular therapies. Table 3 summarizes PHS agency responsibility for Federal oversight/regulation of HPCs.

Table 3. Federal Oversight/Regulation of Hematopoietic Progenitor Cells*			
Source	**Marrow**	**Peripheral Blood**	**Cord Blood**
Autologous	No Federal regulation	FDA regulation as HCT/P	FDA regulation as HCT/P
Related allogeneic (first-degree or second-degree blood relative)	No Federal regulation	FDA regulation as HCT/P	FDA regulation as HCT/P
Unrelated allogeneic	HRSA oversight of Program	HRSA oversight of Program; FDA regulation as HCT/P	HRSA oversight of Program; FDA regulation as HCT/P

*minimally manipulated, for homologous use, and not combined with another article such as a drug or device
HRSA = Health Resources and Services Administration; FDA = Food and Drug Administration; Program = C.W. Bill Young Cell Transplantation Program

Certain HCT/Ps recovered before May 25, 2005 are regulated by FDA under 21 CFR Part 1270, while those HCT/Ps recovered on or after May 25, 2005 are regulated under 21 CFR Part 1271, the current tissue rules in effect as of May 25, 2005. 21 CFR Part 1271 requires establishments that manufacture HCT/Ps to register and list their products with FDA; screen and test donors for relevant communicable disease agents or diseases; and follow good tissue practices to prevent the introduction, transmission, or spread of communicable diseases by HCT/Ps. All foreign establishments importing HCT/Ps to the US also must register and list their products with FDA and follow the applicable regulations. However, it should be noted that the HCT/P regulations apply only to manufacturers, and, for those HCT/Ps regulated solely under 21 CFR Part 1271, the scope is limited to the prevention of transmission of communicable diseases.

HCT/Ps must meet the following criteria, as described in 21 CFR Part 1271.10(a), to be regulated solely under section 361 of the PHS Act (which pertains to the prevention of transmission of communicable diseases):

1. Minimally manipulated
2. Intended for homologous use
3. Not combined with a drug, device or other article (with limited exceptions)
4. Does not have a systemic effect (exceptions are autologous use, use in a first- or second-degree blood relative, or reproductive use).

An HCT/P that fails to meet any one of these criteria and that does not qualify for exceptions specified in the HCT/P rules is subject to regulation as a drug, device, and/or biological product, and additional regulations would apply.

5.2 HCT/P Biovigilance Concerns

Modern day tissue banking was initiated in the U. S. Navy in 1949. Many of today's standards are due to this early experience (52) , as well as the efforts of the American Association of Tissue Banks (AATB) over several decades. AATB has reported substantial growth in tissue recovery and distribution. This is illustrated in Figure 5 and 6 (53).

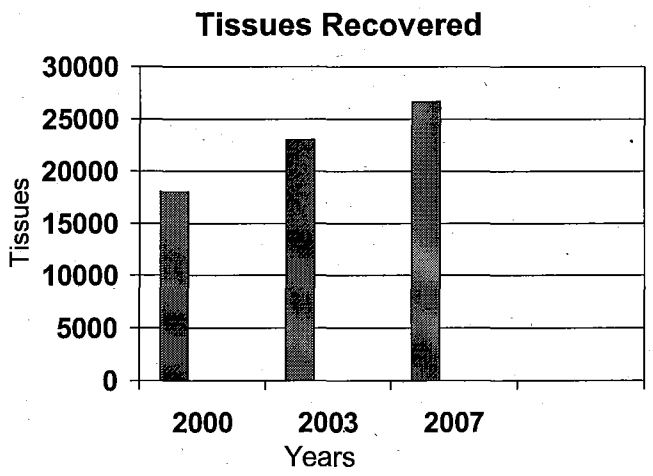

Figure 5. Tissue Donors Recovered in US in the first part of 21st Century

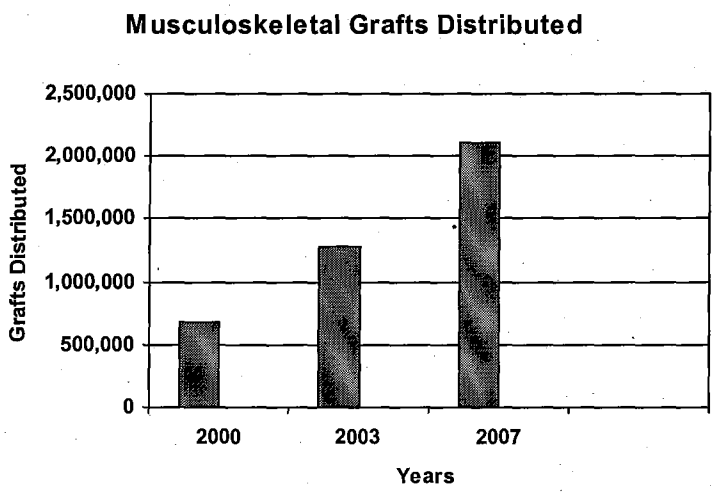

Figure 6. Musculoskeletal grafts distributed in US in the first part of 21st Century

A major difference between blood, organs, and HCT/Ps is that many HCT/Ps undergo processing to disinfect; effectiveness of these methods varies by processor, tissue type, and method employed. Although manufacturers validate their methods and have standard procedures, methods are not required to be FDA approved, and the eventual risk of contamination of final products is not well-quantified, although understood to be quite low for many types of product and disinfection procedures. Better quantification of the potential risk based on the effectiveness of disinfection procedures will help investigators decide if reported infections should be attributed to implanted tissues.

The current understanding of the risk of tissue-associated disease transmission largely is derived from what is learned from case reports. For example, in 2001, CDC investigated a case involving a musculoskeletal tissue allograft recipient who died as the result of clostridium infection from a contaminated graft. In the course of its investigation, CDC identified a total of 14 patients with *Clostridium* infections associated with musculoskeletal tissue allografts from this and other donors (54). As a result of this case, FDA published guidance for immediate implementation that emphasized existing regulatory requirements for the prevention of tissue contamination during processing. In a 2005 article, investigators described transmission of HCV to several organ and tissue recipients from a donor that was antibody negative but later determined to be infected with HCV. This case generated

much publicity because of the numbers of organs and tissues (44 transplants into 40 recipients) produced from this single donor. Through genetic comparison of isolates from donor and recipient serum, investigators determined that 8 recipients (three organ recipients and five tissue recipients) were infected with HCV transmitted by the donor. Two of the tissue recipients and one organ recipient were diagnosed with HCV several months before many of the tissues were transplanted. Some of the subsequent tissue recipient infections would have been prevented if donor transmission had been recognized and communicated to the tissue establishments at the time of diagnosis of the three initial cases (55).

Another issue of significant concern is tracking of HCT/Ps to the level of the recipient. During 2005 and 2006, HHS became aware of two HCT/P recovery firms committing serious violations of Federal regulations. An FDA investigation found that the firms were recovering tissues from donors in a manner that did not prevent the transmission of communicable disease. Other violations included creating and maintaining inaccurate and incomplete records related to: the medical/social history interview with next of kin; medical history, including place, time, and cause of death; and communicable disease screening and testing. These practices presented a danger to public health, and the FDA ordered the firms to cease manufacturing operations and retain tissues in inventory. In the first case, tissue had been sent to a number of processors, then processed, distributed and sub-distributed. Tissues from over 1,000 donors were recovered during a three-year period of time. An estimated 25,000 tissues were distributed to hospitals and other healthcare providers in the U.S. and internationally for transplantation. The magnitude of distributions puts in perspective the current difficulties of timely tracking of HCT/Ps, something that is particularly important when there is concern about safety. A system such as the recently piloted Transplantation Transmission Sentinel Network (to be described in Section 6.1) may help to address issues related to tracking.

5.3 Efforts in HCT/P Biovigilance

5.3.1 Global Biovigilance

Development of vigilance and surveillance systems for tissues and cells used in transplantation is a recent undertaking in most of the world. The European Union Standards and Training for the Inspection of Tissue Establishments (EUSTITE), co-funded by the European Commission, is assisting member states by providing guidance documents and training in the areas of inspection and adverse event and reaction reporting for tissue and cells. The project is developing vigilance and surveillance tools consistent with and complimentary to those existing, such as hemovigilance systems,

and under development globally, led by the Department of Essential Health Technologies at the WHO. A survey completed in January 2007 on the status of such systems found that 10 member states had a reporting system in place, while the other 17 member states still have not established reporting systems, although a few were currently planning their systems and would be launching their systems shortly. Member states gave various responses regarding the types of adverse events/reactions which would be considered to be reportable in their member states.

Health Canada requires that source establishments investigate and submit reports of certain adverse reactions, errors, and accidents involving cells, tissues, and organs to the Canada Vigilance Program. Health professionals and consumers also may submit voluntary reports to the Canada Vigilance Program.

The Center for International Blood and Marrow Transplant Research (CIBMTR), a division of the Medical College of Wisconsin, brings together the International Bone Marrow Transplant Registry and the Autologous Blood and Marrow Transplant Registry (IBMTR/ABMTR) and the NMDP to facilitate large clinical studies of blood and marrow transplantation. Through CIBMTR, researchers have access to large clinical databases on autologous, related, and unrelated donor HPC transplants. CIBMTR reports that 50,000 transplants are performed worldwide annually, and about two-thirds are autologous.

5.3.2 HCT/P Biovigilance in the United States

5.3.2.1 Federal Reporting

An adverse reaction, as defined in 21 CFR Part 1271.3(y), means a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response. HCT/P manufacturers must investigate any adverse reaction involving a communicable disease related to an HCT/P they made available for distribution. Manufacturers must report to FDA an adverse reaction involving a communicable disease if:

- Fatal
- Life-threatening
- Causes permanent impairment/damage, or
- Necessitates medical or surgical intervention

For reportable adverse reactions, manufacturers must submit a report through FDA's MedWatch Adverse Event Reporting Program within 15 days of receipt of information about the reaction. Manufacturers must submit a follow-up MedWatch report within 15 days of receipt of new information from

the investigation. The adverse reaction reporting requirements apply only to products recovered on or after May 25, 2005 (the effective date of the current tissue rules). Manufacturers are encouraged to submit voluntary reports related to products recovered prior to May 25, 2005, as well as product problems that do not involve infectious disease transmission. Manufacturers are not required to report adverse reactions that do not involve infectious disease.

The definition of an adverse reaction requires that a manufacturer decide that there is a reasonable possibility that the HCT/P caused the response. It is likely that different manufacturers have different thresholds for attributing causality to the HCT/P. Also note that, while HCT/P manufacturers are required to report serious adverse reactions to FDA, reporting is voluntary for clinicians. Clinicians are encouraged to submit reports directly to the manufacturer and to FDA through the MedWatch program, but underreporting is likely. Manufacturers may remain unaware of safety issues if clinicians fail to report cases.

Factors such as an infection with an unusual organism or temporal proximity between implantation and onset of infection may suggest that the HCT/P could be the cause. However, it often is difficult for clinicians to distinguish between a graft-attributable infection and an unrelated post-operative infection. If infections are reported to the manufacturer or FDA, a full investigation that includes review of donor and manufacturing records still may fail to produce evidence linking the HCT/P to the infection, particularly for common organisms. Certain information could implicate the HCT/P as transmitting the infection such as: similar infections reported in more than one recipient of HCT/Ps from the same donor; a very unusual organisms identified in pre-processing (recovery) cultures and the recipient; contamination in the processing environment with the same organism; or evidence of the same infection in the HCT/P donor. However, in the absence of factors such as these, as is the case for most reported infections, the cause of the infection is indeterminate.

In 2004, CBER formed the Tissue Safety Team (TST), composed of representatives from several offices within the center. The TST was formed to provide a coordinated process for the review, analysis and follow-up of adverse reaction reports received by CBER; to efficiently and effectively respond to emergencies; and to strategically identify policy and outreach needs and opportunities and implement solutions. A subgroup of the TST evaluates every MedWatch HCT/P adverse reaction report submitted (56). For reports involving infections in HCT/P recipients, TST generally contacts the HCT/P manufacturer for donor and processing related information and, if additional data is needed on the clinical case, the recipient's transplant

surgeon or other health care professional involved in the case. As needed, the TST collaborates with points of contact at other offices within FDA (such as OBRR when the HCT/P donor or recipient received blood or blood products), and other HHS agencies (such as CDC and HRSA).

HCT/P manufacturers also must investigate all deviations related to a distributed HCT/P for which they performed a manufacturing step. They must report to FDA, within 45 days of the discovery of the event, those deviations related to core CGTP requirements (specified in 21 CFR Part 1271.150(b)). The term "HCT/P deviation" is defined in 21 CFR 1271.3(dd) as an event that represents a deviation from applicable regulations or from applicable standards or established specifications that relate to the prevention of communicable disease transmission or HCT/P contamination; or that is an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease or may lead to HCT/P contamination. Deviations must be reported to the Director of the Office of Compliance and Biologics Quality in CBER on a standardized BPDR form (Form FDA-3486).

FDA's Center for Devices and Radiological Health (CDRH) launched the Medical Product Safety Network (MedSun) in 2002 to identify and share information about problems with the use of medical devices. MedSun (www.medsun.net) is a targeted surveillance program that involves AE reporting from a sentinel network of around 350 healthcare facilities throughout the country. FDA currently is operating a sub-network involving a subset of MedSun sites, called TissueNet, for the reporting of adverse reactions and other events related to HCT/Ps. TissueNet is the first enhanced surveillance program for HCT/P-related adverse reactions and boosts the numbers of voluntary reports submitted for these products. MedSun sub-networks like TissueNet build relationships between MedSun/FDA and the front-line product users in specific "high-risk" clinical care areas. TissueNet enhances CBER's understanding of the use of HCT/Ps and provides a resource for communication with the clinical tissue and cell transplant community. The objectives are to describe the frequency and types of reports following HCT/P transplants; identify potential causes or "near misses"; and improve the safety of HCT/Ps. TissueNet sites use MedSun to report HCT/P-related AEs or product problems to FDA via a secure, internet based data entry portal. The data entry screens are based on items on the MedWatch Form, and MedSun translates the data into a completed MedWatch form. The first report from this system was generated in 2005 and the project is funded to operate through September 2009.

5.3.2.2 Private Sector Reporting

Several professional organizations also perform tissue biovigilance activities. Federal agencies collaborate with these organizations to foster harmonization of standards and the exchange of information to address safety issues. Some of these efforts are described below.

The Joint Commission (TJC) accredits and certifies more than 15,000 healthcare organizations and programs in the US. In 2005, TJC published standards related to tissue storage and issuance. These standards require the assignment of responsibility for handling tissue within a hospital to a single coordinating entity. The oversight responsibility includes: supplier certification; incoming inspection and logging in of tissue; traceability and recordkeeping; storage temperature monitoring; investigation of adverse outcomes; reporting tissue related infections to the tissue supplier; sequestering tissue reported by the supplier as contaminated; the notification of surgeons and recipients if tissue donors are subsequently found to harbor infection; and compliance with federal and state regulations if supplying tissues to any other facility. The College of American Pathologists has adopted similar standards.

Many hospitals have turned to their blood bank where many of the capabilities for tissue management already exist. As a result, the AABB established a tissue task force to begin to develop guidance documents and assistance to hospital blood banks to prepare for managing tissue within their facilities. The AABB Tissue Task Force, which later in an attempt to better understand how tissues were being managed within hospitals, prepared and distributed a survey to hospital institutional members. The survey contained questions on tissue types handled, the breadth of responsibility, and facilities within hospitals responsible for tissue. Of the 904 institutional members invited to participate, 402 gave interpretable responses; 325 reported the use of allogeneic or autologous human tissue. The survey indicated that the department of surgery was the most likely hospital department to have any responsibility for tissue use, followed by the blood bank. Surgery departments were most frequently responsible for tissue handling, documenting use, and for adverse event reporting; for the latter category only 23% reported infection control responsibilities (57).

The AABB survey was corroborated by the 2007 NBCUS that of hospitals reporting, 14% responded that blood banks and 80% responded that operating rooms had responsibility for tissue management (36). Adverse events were reported in this survey. Although limited to hospital transfusion service data on facility events, there were 43 AE reports, including bacterial and viral infections and graft failures, from 229,115 grafts implanted for a

rate of 1:5,300. Since healthcare facilities do not have reporting requirements (unless they are performing a manufacturing step and subject to FDA reporting regulations), one is left to extrapolate the actual number of AEs occurring.

The AATB has been publishing standards since 1984. AATB Standards state that tissue banks establish policies and procedures regarding adverse outcomes and recalls, and have a process for sharing information with other tissue banks known to have recovered or received tissue from the same donor. Tissue banks must document and investigate all reported or suspected adverse outcomes potentially related to an allograft. Tissue banks must assure that tissue can be tracked to the consignee, and must notify the consignee of its responsibility to maintain records traceable to the recipient. Typically, tracking to the recipient is facilitated through graft implant cards that accompany each allograft that is distributed. These cards contain information about the graft, and space for recording information about graft use (such as facility, surgeon, and recipient). Manufacturers ask hospitals and healthcare providers to return these records following transplants, but there is no enforceable requirement for the return of the implant cards. Compliance with return of these cards varies considerably from bank to bank depending on the degree to which the tissue bank pursues their return. A recent AATB survey, to which only 15 of over 100 banks responded, reported an average return rate of just over 50% with a wide range from less than 10% to as high as 95% (53). Information about graft disposition and adverse outcomes can provide context for assessing the potential risk of tissue allograft transplantation.

The Eye Bank Association of America (EBAA) implemented its Medical Advisory Board (MAB) in 1991 in response to a 1990 requirement for all eye banks to seek three to twelve month follow-ups of all patient outcomes. EBAA's Online Adverse Reaction Reporting System (OARRS) was redesigned in 2005. The MAB reviews results on a biannual basis. Eye banks provide institutions with self-addressed envelopes to complete and return follow up forms. Persons who submit reports on OARRS must provide information on the adverse reaction, surgery, microbiology results, tissue mate status, donor, and method of transporting the tissue from the source eye bank.

HRSA awarded CIBMTR a contract to establish and maintain the Stem Cell Therapeutic Outcomes Database (SCTOD) component of the C.W. Bill Young Cell Transplantation Program. Transplant centers must submit data annually to CIBMTR on all allogeneic transplant recipients. Although most data are focused on outcomes, some data also relate to adverse events such as early and late graft failures, risk factors for graft versus host disease

(GVHD), prevalence of microbiologically contaminated hematopoietic stem cell products, antibodies to the graft, infections and second cancers.

NMDP collects data on donor adverse events and post-donation symptoms (Appendix 5 and 6). Data collected include serious and minor complications following marrow and peripheral blood stem cell collections, such as mechanical injury to tissue, anesthesia reactions, infection, seizures, excessive pain and delayed return to normal work functions. Minor side effects such as hypotension, syncope and collection site pain are reported in 75% of marrow donors. Peripheral blood stem cell (PBSC) donors are also monitored for adverse events specific to filgrastim administration and central intravenous catheter placement, such as more serious degrees of headache, fatigue, bone pain, hypotension, vomiting, central line placement complications, or more serious cytopenias. HRSA personnel are informed of adverse events that are serious and unexpected and FDA is also notified if a serious and unexpected adverse event occurs in a PBSC donor.

5.4 Gaps in Current HPC/T Adverse Reaction Reporting Systems

Gap 9: Limited information on the potential for HCT/Ps to transmit infectious disease

Risks of disease transmission by HCT/Ps are not well characterized for all known and emerging communicable disease agents, and for all types of cell products and tissues. Improvements in donor screening and testing, and in methods for processing some tissues, have made these products safer than in the past. However, un-quantified risks remain.

Gap 10: Ability to ascertain whether reported infections in HCT/P recipients can be attributed to the tissue is limited.

Post-operative infections occur at a small but appreciable rate, independent of allograft use. The majority of reported infections in HCT/P recipients are likely due to local contamination or some other cause typical of post-operative infections and not attributable to the HCT/P. Although each report deserves thorough evaluation, this leads to a low predictive value for a given report.

Infections with common organisms are particularly difficult to attribute to implicated HCT/Ps. Multiple recipients with infections involving the same organism would suggest potential HCT/P-related transmission and require further evaluation.

Gap 11: Regulations concerning HCT/P adverse reaction reporting do not extend to the level of the healthcare facility or healthcare provider

The HCT/P regulations apply only to manufacturers; hospitals and healthcare providers (e.g. transplant surgeons, dentists) are not required under these regulations to report adverse reactions experienced by their patients who received HCT/Ps. Surveillance for recipient infection depends largely on voluntary reporting by clinicians, and it is likely that an unknown number of events are undetected and/or unreported. HCT/P manufacturers are unable to investigate adverse reactions of which they are not aware.

Although TJC tissue standards include reporting of adverse events, compliance with the reporting standards is not enforced and TJC standards do not extend to physician and dentist offices or other facilities not accredited by TJC.

Gap 12: Current mechanisms for tracking HCT/Ps to the level of the recipient are limited.

Tissue establishments request that healthcare providers convey back to them information about the final disposition of the graft; e.g. through return of graft implant cards. However, hospitals and healthcare providers are not subject to enforcement actions for failure to convey this information. Voluntary compliance with return of implant cards is relatively low in some cases. Lack of information about final graft disposition hinders investigation of adverse reactions and allograft recalls.

Gap 13: Adverse reaction reporting for HCT/Ps regulated solely under Section 361 of the PHS Act is limited to infectious diseases

The scope of adverse reaction reporting required for HCT/Ps regulated solely under the authority of Section 361 of the PHS Act is limited to the prevention of transmission of communicable diseases. HCT/P manufacturers are not required to report adverse reactions that do not involve potential transmission of a communicable disease, and healthcare facilities and healthcare providers are not required to submit any reports. However, reports of non-infectious events potentially could reveal other safety concerns.

Gap 14: Information about adverse reactions in other recipients of HCT/Ps from an implicated donor may not be readily available

HCT/Ps recovered from a single donor may be sent to multiple establishments for processing. While FDA regulations require that manufacturers maintain complaint files related to HCT/Ps they made available for distribution, this information may not be readily available to other manufacturers of HCT/Ps from the same donor.

6.0 BIOVIGILANCE EFFORTS IN THE US: ADVERSE EVENTS ASSOCIATED WITH SOLID ORGANS

6.1 Solid Organ Adverse Event Reporting

Transmission of infectious agents, both known and unknown, from an organ donor represents a particular hazard to the transplant recipient because, unlike a recipient of blood transfusion, the immunosuppression regimen (required to prevent organ rejection) weakens the patient's host defense mechanisms against invading organisms. The resulting infection is thus more likely to result in devastating, and sometimes fatal, consequences. As such, biovigilance takes on added importance in the setting of solid organ transplantation. Although it is estimated that the risk of acquiring an infectious disease through organ transplantation is an infrequent occurrence, it is still higher than through blood or tissue transplantation. This risk is balanced against the life saving indications for transplantable organs and the substantial number of patients that die each year due to the lack of organs.

There is a need to capture more complete data on transmission of infectious diseases and malignancies of donor origin. Several factors make the task of identifying potential transmissible infections in deceased solid organ donors more problematic than for blood donors: (1) information about medical history and social/behavioral risk factors of deceased organ donors is often incomplete and suboptimal (usually obtained from family or acquaintances); (2) potential organ donors are typically admitted to the hospital emergently with catastrophic medical or traumatic events, and may receive multiple transfusion products with the small risk of transfusion transmitted disease; (3) organ recovery often is done urgently (due to the donor's deteriorating clinical status) and the retrieved organs must be transplanted within hours of recovery, limiting the amount of time available to obtain the results of donor screening tests or perform extensive confirmatory lab testing of any abnormal test results prior to transplant of the organs; and (4) because the number of patients waiting for organ transplants far exceeds the number of available organs, it is important that screening tests for infectious agents in a potential organ donor are accurate to avoid unnecessarily discarding useable organs. In addition, because of the limited supply of organs, even individuals known to have risk factors for infectious diseases may be accepted as organ donors. Hence, the transplant community, including potential transplant patients, must balance the risk of acquiring an infection or other disease from a potential donor against the potential for death or morbidity if an organ from a particular donor is rejected.

The HRSA, Division of Transplantation oversees the transplantation of human organs, including kidney, liver, heart, lung, pancreas, and intestine.

The National Organ Transplant Act (NOTA) of 1984 established the Organ Procurement and Transplant Network (OPTN), resulting in a national computerized system to maintain a waiting list and allocate organs, including a 24 hour organ-recipient matching operations center. In 1986, the United Network for Organ Sharing (UNOS) was awarded the first contract to operate the OPTN, and has held the contract since then through a competitive award process. UNOS has developed an online database system, called UNet for the collection, storage, analysis and publication of all OPTN data pertaining to the patient waiting list, organ matching and transplants. The OPTN final rule became effective in March of 2000. The rule established a regulatory framework for operation of the OPTN, including requirements for policy development and member compliance with these policies, including policies consistent with the recommendations of the Centers for Disease Control and Prevention for the testing of donors and follow-up of transplant recipients to prevent the spread of infectious diseases. The Division of Transplantation of HRSA also administers the Scientific Registry for Transplant Recipients contract, as well as various grant programs and initiatives to increase organ donation and transplantation.

Through its oversight role, HRSA monitors the activities of the OPTN to include member compliance with NOTA, the OPTN Final Rule and other applicable Federal law. The OPTN Final Rule requires the OPTN, with the assistance of the OPTN contractor, to review member compliance with Federal law and regulations and the policies and bylaws of the OPTN. The OPTN, with the assistance of the OPTN contractor, is also required to conduct periodic and special compliance reviews of OPTN members. Members that are not found to be in compliance are referred to the Membership and Professional Standards Committee (MPSC) for review. Unlike the on-site inspections conducted by the professional State Facility Surveyors under CMS, much of the OPTN oversight, generally carried out through confidential peer review conducted by the MPSC, may also conduct on-site peer reviews with audit teams. The OPTN has the authority to take certain actions against OPTN members that are not in compliance, including issuing letters of warning, letters of admonition, letters of reprimand; placing the member on 'Probation' and making the member a 'Member Not in Good Standing.' Both 'Probation' and 'Member Not in Good Standing' are public actions, which in the case of transplant programs, may impact the program's ability to receive contracts from insurance companies. In addition to actions that may be taken by the OPTN, particularly egregious non-compliance issues may be referred by the OPTN Board of Directors to the Secretary of HHS for further action, including removing a transplant program's ability to receive donor organs and ability to participate in Medicare and Medicaid.

Solid organ transplant programs that participate in the Medicare program are required by the CMS to comply with the following Conditions of Participation (per 42 CFR Part 482.96) regarding Adverse Events:

The actual regulations, 42 CFR 482.69(b), are as follows: (b) *Standard: Adverse events.* A transplant center must establish and implement written policies to address and document adverse events that occur during any phase of an organ transplantation case.

1) The policies must address, at a minimum, the process for the identification, reporting, analysis, and prevention of adverse events.
2) The transplant center must conduct a thorough analysis of and document any adverse event and must utilize the analysis to effect changes in the transplant center's policies and practices to prevent repeat incidents.

The regulation clearly states that "unintended transmission of infectious disease to a recipient" is an example of an Adverse Event under "Definitions" in 42 CFR 482.70.
CMS has various options at its disposal to ensure transplant program compliance with these Conditions of Participation.

In response to increasingly recognized adverse events due to diseases transmitted through organ transplantation, there are relatively new policies in place to require reporting of suspected disease transmission. These efforts include the creation of an OPTN/UNOS Disease Transmission Advisory Committee (DTAC) to facilitate and monitor reports of organ donor-derived diseases in organ recipients; the reports are required under new OPTN/UNOS policy. As a result, documented incidence has increased every year since reporting has been required and in 2007 the donor-derived disease transmission incidence was 0.96% of deceased donor donations. (58)

Recent CDC investigations have identified causes of multiple illness clusters in organ transplant recipients, including WNV, rabies, LCMV, Chagas disease, and tuberculosis. Following these investigations of disease transmission events associated with transplantation, CDC sponsored an organ and tissue safety workshop in 2005 to promote a better communication network within and between the organ and tissue community. From that workshop came a number of recommendations to both government and the tissue/organ community, including the development of a unique donor identification system linking organs and tissues, clear mechanisms for adverse event reporting by health-care facilities, stronger information dissemination systems to a broader array of clinicians and health professionals as well as patients, and a notification algorithm for trace-back

and trace-forward tracking. This system, developed by UNOS and other organ and tissue community partners in a cooperative agreement with CDC, is called the Transplantation Transmission Sentinel Network (TTSN). The purpose of the network is to provide a system for detecting emerging infections among organ and tissue allograft donors and recipients and aid healthcare personnel in detecting, communicating, tracking and preventing the transmission of infections.

To guide its development, UNOS organized a TTSN Advisory Committee made up of organizations with a stake in this process. The Advisory Committee identified five key parts for development of a working communication network: registration or search for donors (Part A); registration of recipients (Part B); reporting of adverse events (Part C); dissemination of information to appropriate regulatory and public health agencies (Part D); and education within the community (Part E). In addition, UNOS identified a group of tissue banks, eye banks, organ procurement organizations, and healthcare facilities to pilot the system. After piloting, a quality assessment will be performed to evaluate the development process and to determine next steps for national implementation. The national implementation of systems to enhance tracking and communication concerning adverse events involved organs and tissues, such as TTSN, will be an important step forward in allograft patient safety.

Three recent changes in organ donor procurement practices and transplantation have heightened interest in an effective nationwide biovigilance system that includes solid organ transplantation.

First, due to the ever-expanding waiting list of patients in need of transplantable organs, deceased donors with various behavioral and social risks, which would categorized them as "high risk" donors, are being accepted with the expectation that all available information will be provided to all involved. Although donors are screened and tested for infectious diseases, the inherent limitations of less-than-perfect screening tests for infectious agents have increased the potential for missing a potentially serious infection in such "high risk" donors. Screening tests are not identical to those used in blood and tissue donors, in part because of concerns over timeliness and false positive results, potentially impacting availability. A fully operational nationwide biovigilance system can improve the capabilities to detect and respond swiftly to such transmissible agents when these events occur thus minimizing the consequences in all recipients of organs from that affected donor.

Second, in an attempt to further increase the number of organs, especially kidneys, available from individuals with a demonstrated wish to donate, the transplant community is pursuing organ procurement following cardiac arrest and failed cardiopulmonary resuscitation in both the hospital and community settings. This has been termed Uncontrolled Donation after Circulatory Death (UDCD) or Donation after Cardiac Death (DCD). In these still infrequent situations, it may be difficult to procure suitable screening test specimens prior to death. How this might affect disease transmission from UDCD solid organ donors remains to be seen.

Third, a recent advance in the field is the transplantation of vascularized composite allografts (VCA), a variety of body parts composed of multiple types of tissues transplanted as an anatomical unit. The most notable types of VCAs to date have been hand and face transplants. Given the anticipated increase in VCA transplants, HRSA published a Request for Information (RFI) on March 3, 2008 in the Federal Register for the purpose of soliciting feedback from stakeholders and the public as to whether VCAs should be included within the definition of organs covered by the OPTN final rule and/or added to the definition of human organs covered by section 301 of NOTA (73 Federal Register 11420). Through this RFI, HRSA invited the public to attend a meeting on April 4, 2008 to discuss the issues described above. The meeting provided a venue for interested stakeholders to provide input and generate discussion. Interested parties were invited to submit written comments to HRSA by July 2, 2008. Further action is still pending at this time. Federal authorities must determine the appropriate level of oversight/regulation to address safety concerns without unduly restricting access.

6.2 Gaps in Current Organ Adverse Reaction Event Reporting Systems

Gap 15: Lack of nationwide common organ/tissue donor network system for real-time reporting, data collection, communication, and analysis of donor transmitted diseases in organ and tissue transplant recipients, including a common donor identifier necessary for linkage back to implicated donor of both organs and tissues

One donor may provide organs and tissues to be used in dozens of recipients. Currently there is no unique donor identifier that links a common donor for both organs and tissues. While the OPTN uses a unique donor identifier for each organ donor, and FDA requires a unique donor identifier for each tissue donor, these organ and tissue donor identifiers are not necessarily the same. A unique donor identifier that links all of the organs and tissues from a

common donor may facilitate the rapid identification of all allografts from that donor in the event of a public safety concern.

Although the recently implemented OPTN DTAC now facilitates real-time coordination of communication and notification of potential donor transmitted diseases (including infections and malignancies) for organs, there is still some time lag between incident identification, event reporting, notification, and follow up. Also, a nationwide reporting network for organ and tissue events may aid tissue establishments in sharing information pertaining to potential disease transmissions identified in tissue recipients.

There currently is no published comprehensive analysis of the prevalence and incidence of various diseases in organ donors as there is for blood transfusions. Implementation of a nationwide common organ/tissue donor system, such as TTSN, would facilitate a comprehensive analysis of the prevalence and incidence of various diseases in these donors and the potential for transmission to recipients. Although it is estimated that the risk of acquiring an infectious disease through organ transplantation is higher than through blood or tissue transplantation, this risk is balanced against the life saving indications for organ transplantation and the substantial number of patients that die each year due to lack of organs.

Gap 16: No Requirement to retain donor and recipient samples

Given that several factors make the task of identifying potential transmissible infections in deceased organ donors difficult (such as inaccurate medical/social history, incomplete donor testing prior to transplantation of the organs), it would be valuable if retained donor and recipient specimens were available for testing. Although OPOs and transplant hospitals do keep these specimens for various lengths of time following organ procurement and transplant surgery, there is no requirement for specimen retention and current retention practices are variable. There is no system with a consistently applied uniform policy for specimen retention time, storage, and retrieval capable of supporting a nationwide biovigilance program.

Having acknowledged these recognizable gaps identified above, it is important to keep the potential for donor-transmissible disease in context with respect to the life-saving benefit these organs provide for severely ill patients waiting for transplant. Humar and Fishman (59) sum it best:

> *"First, it should be emphasized that these events continue to be very uncommon and that current screening practices have a remarkable track record for maintaining safety in*

transplantation, considering the number of potential organ and tissue donors that are screened each year. Second, we should realize that the screening of organs for pathogens is about risk mitigation and not about risk elimination. It is unlikely we will ever be able to completely eliminate the risk of disease transmission associated with transplantation. Such a goal is unrealistic with present technology. However there is room to improve donor screening and the detection of such events when they occur, to improve communication regarding transmission events, and to deploy therapies and public health investigations more quickly than is possible at present. The process of donor screening must continue to evolve with our knowledge about the ever-changing field of infectious diseases."

7.0 POLICY CHALLENGES

7.1 Historical Background

Blood establishments in the US were launched after World War II in many communities to support the medical needs of the local populations. As a result of this community approach, the US blood supply became isolated and fragmented. In the 1970's, HHS, then called the Department of Health, Education and Welfare, attempted to establish a national blood policy to unify a national strategy for blood safety and availability. However, the private sector was very concerned about the potential impact of a national blood policy and a policy was never established. The previously proposed national blood policy was reviewed by the ACBSA in January 2004 and the Committee acknowledged the draft policy generally captured many of the present day concepts. However the US still is without a national blood policy although there are FDA regulations codified to ensure Good Manufacturing Practices.

The infrastructure for policy on solid organ transplantation, organ recovery, and equitable allocation of organs through a single national network (i.e., OPTN) was founded in Federal legislation through the National Organ Transplant Act (NOTA), enacted in 1984.
This legislation was amended in 2000 (60). In accordance with the NOTA, policy in the organ transplantation community is established by the OPTN and if it is to be enforceable the policy must be approved by the Secretary of HHS. The only policy currently approved by the Secretary and enforceable under Federal law is reporting of data on Office of Management and Budget (OMB) forms. These data are on transplant candidates, recipients and all living and deceased donors. Within the organ transplantation community, oversight of policy and bylaws by the OPTN is recognized as key to a successful solid organ transplant program in the US. The current oversight system relies on confidential peer review of compliance in contrast to policy enforcement (61).

Human tissue became regulated under FDA in 1993. FDA's current rules for HCT/Ps, in effect since 2005, are more comprehensive than the earlier rule. They cover a wider range of tissues and cellular products, including, for example, reproductive tissues and HPCs, a more extensive and continually updated list of relevant communicable diseases, and require registration of all establishments that manufacture HCT/Ps in the US or for import to the US as well as compliance with Current Good Tissue Practices. Reporting requirements under the new rules include mandatory reporting of manufacturing deviations and adverse reactions relating to communicable disease transmission.

The Stem Cell Therapeutic and Research Act of 2005 (Stem Cell Act 2005) was passed by Congress and signed by President Bush in December 2005 as Public Law 109-129. The Stem Cell Act 2005 is managed by HRSA. The Stem Cell Act 2005 includes the C.W. Bill Young Cell Transplantation Program and the National Cord Blood Inventory (NCBI). The cell transplantation program is named after Congressman C.W. Bill Young who is a long-time supporter of bone marrow transplantation and helped start the National Bone Marrow Donor Registry. The C.W. Bill Young Cell Transplantation Program expands upon the previous requirements to increase the number of marrow donors and cord blood units and continues to serve patients who need a bone marrow or cord blood transplant. The NCBI will also provide cord blood units for research.

7.2 Mandates for a Comprehensive Biovigilance Program

The rapid growth and evolution in the scientific and technical fields of transfusion and transplantation call for a comprehensive biovigilance program. Specifically, AE monitoring for recipients and donors, quality assurance, and emerging threat assessment are critical components in a comprehensive system. As identified in this report, the AE reporting can either be active or passive depending on timeliness of data collection and analysis. Ideally, all adverse events and outcome reporting should be active in terms of data collection but this may not be practical in all sites nationally for every product.

7.3 Mandatory vs. Voluntary Adverse Event Reporting

For blood and blood products, there is a robust regulatory structure from collection to transfusion and accrediting organizations active in emphasizing patient safety, but coordinated surveillance for AE event policy on reporting, particularly for non-fatal events, is lacking, both in donors and in recipients. For other tissues (i.e., HCT/Ps), regulation is narrower in scope, being limited to control of communicable diseases, but with no government regulation extending to the end user in the clinical setting.

Common processes for data collection, analysis and evaluation are either lacking or underdeveloped in both the private and public health communities. Compounding the lack of common processes is the lack of understanding of transfusion and transplant safety risks across the spectrum of products.

Surveillance for a wider array of AE is needed for blood and blood products. Voluntary reporting of AE may increase reporting if there are no punitive consequences to the facility, but such systems must be implemented widely to

have an impact. CDC's NHSN hemovigilance module is expected to have such as impact. In addition, serious AE reporting required by the proposed Safety Reporting Rule (SRR) will help broaden the hemovigilance data that FDA collects.

Mandatory reporting for HCT/P manufacturers, excluding reproductive tissue establishments, consists of adverse reaction reports involving communicable disease transmission, and deviations in manufacturing that may introduce risks of communicable disease transmission or contamination. For HCT/Ps also regulated as licensed biologics, mandatory reporting requirements are more extensive. Under the MedWatch program, FDA receives voluntary reports of other types of adverse events from healthcare providers and recipients.

Finally, for solid organs, for which transmission risks are highest, oversight mechanisms feature an excellent database infrastructure through the OPTN, but such systems currently are focused on patient outcome, not disease transmission or other adverse events. A system such as the prototype TTSN attempts to strengthen connections between organ and tissue recovery organizations and healthcare providers to solve multiple problems simultaneously. However, TTSN is unlikely to be successful as a purely voluntary system without specific resources allocated for implementation.

7.4 Public/Private Partnership

Industry, led by AABB, initiated its efforts at collaboration on biovigilance at about the same time biovigilance was incorporated into the ACBSA recommendations (September 2005 and August 2006) as a priority for a federal government national strategic plan. In addition CDC and UNOS recently completed a cooperative agreement to develop a prototype for surveillance of transplant-transmitted diseases, the TTSN. Progress made by government and industry has created valuable momentum toward a lasting public-private partnership in this area. However, although current initiatives for blood, organ, and tissue safety, such as HHS partnerships with AABB and UNOS, represent a potential to fill gaps for blood, organs, and some HCT/Ps, resources are lacking for system maintenance and expansion.

7.5 Conclusions

Blood products, organs, and HCT/Ps are obtained and managed by independent local blood collectors, organ procurement organizations, and tissue establishments. Federal oversight includes monitoring through facility inspections or accreditation, e.g., by FDA, CMS or CMS granted deemed status by an accrediting organization. Industry generally supports safety

efforts, but encourages the Federal government to minimize requirements to reduce burden and duplication of efforts. Thus, voluntary reporting of AE would be more palatable but may hinder implementation of biovigilance without adequate enforcement.

A uniform biovigilance system may not be possible in the US, given differences in oversight and regulation of these different products, but these differences should not be an obstacle to a common coordinated national program. Therefore, a concerted effort is needed for coordination among PHS agencies in the federal government and organizations in the private sector to assure safe and available transfusion and transplantation. Systems need to avoid overlap in order to minimize reporting burden. However, mandatory regulatory components alone will not be sufficient, as data cannot be shared from these sources, emphasizing the need for voluntary non-regulatory components in parallel. Uncoordinated efforts without a clear governance plan may be the greatest threat to patient safety related to biovigilance, as progress may cease. Importantly, systems need to be aligned with FDA, HRSA, and CMS reporting requirements and AHRQ-mandated PSO data elements to minimize data reporting burden; public health surveillance should be coordinated with CDC; research priorities should be coordinated with NIH.

A comprehensive biovigilance program should bridge both regulatory and organizational gaps to meet public health needs. The first step is to develop a new HHS action plan that includes blood, HCT/Ps, and organs. The absence of a road map for HHS is a notable deficiency, and stalls momentum for its agencies (i.e., AHRQ, CDC, CMS, FDA, HRSA, and NIH) to develop their own strategic plans. Regular assessment and evaluation of current measures is needed to determine risks to patient safety. Disease transmission and other adverse events associated with transfusion and transplantation constitute risks that are evident but unevenly quantified, depending on the biologic. Although patient safety is paramount, the need to assess availability also needs to be taken into consideration.

After a strategic plan for biovigilance is developed, to assure the appropriate scope, participation, and a common architecture, details can be finalized on the resources and partners needed to accomplish the task. Well-defined transparent governance of a private/public partnership for biovigilance is in the best interest of the American people.

7.6 Recommendations

Given these policy challenges, the PHS Biovigilance task group developed the following recommendations:

1. We recommend government resource support for a national biovigilance program to monitor and enhance safety of blood, organs, and HCT/Ps.

2. We recommend integration of systems within the government and those within the private sector, involving blood, organs, and HCT/Ps, including all related voluntary and mandatory adverse event reporting systems.

3. We recommend steps to enhance mechanisms for surveillance, including sentinel reporting and investigation, and comprehensive surveillance that features benchmarking.

4. We recommend developing an HHS action plan to support the above three recommendations.

END OF REPORT TEXT

8.0 APPENDICES

APPENDIX 1: Blood Action Plan

ACCOMPLISHMENTS TO DATE

FY97

- Team Biologics – Insuring Compliance of Plasma Fractionators, 10/97
- FDA Response to Emergencies and Class I Recalls, 10/7/97
- Workshop: Potency and Dosage of Von Willebrand Factor Concentrates, 9/26/97
- Workshop: The Biologics License Application (BLA) for Blood Products and Reporting Changes to an Approved Application, 12/2/97
- Workshop: Current Topic in Immunohematologic Testing, 12/10/97

FY98

- Draft Guidance for Industry: In the Manufacture and Clinical Evaluation of In Vitro Tests to Detect Nucleic Acid Sequences of Human Immunodeficiency Virus Type 1, 7/10/98
- Draft Guidance for Industry: Current Good Manufacturing Practices for Blood and Blood Components: (1) Quarantine and Disposition of units from Prior Collections from Donors with Repeatedly Reactive Screening Tests for Antibody to Hepatitis C Virus (anti - HCV); (2) Supplemental Testing, and the Notification of Consignees and Blood Recipients of Donor Test Results for Anti-HCV, 9/23/98
- Draft Document: United States Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components using ISBT 128, 11/27/98
- Draft Guidance for Industry: Gamma Irradiation of Blood and Blood Components: A pilot Program for Licensing, 12/8/98
- Workshop: Nucleic Acid Testing for HCV and other Viruses in Blood Donors, 9/16/98
- Workshop: Evaluation of In Vivo Efficacy of Platelet Transfusion Products and Platelet Substitutes, 9/28/98
- Workshop: Blood Donor Suitability, 11/23/98
- Workshop: Pilot Program for Streamlining the Licensure of Blood and Blood Components. 2 Topics: Gamma Irradiation/RBC Immunization, 12/9/98

FY99

- Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls (CMC) and Establishment Description Information for Human Plasma-Derived Biological Products, Animal Plasma or Serum-Derived Products, 2/17/99
- Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls (CMC) Information and Establishment Description Information for a Biological In Vitro Diagnostic Product, 3/8/99
- Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls (CMC) Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and for the Completion of the FDA From 356h, 5/10/99
- Direct Final Rule and Companion Proposed Rule: Revisions or Requirements Applicable to Albumin (Human), Plasma Protein Fraction (Human), and Immune Globulin (Human), 5/14/99
- Draft Guidance for Industry: Current Good Manufacturing Practices for Blood and Blood Components: (1) Quarantine and Disposition of Prior Collections from donors with Repeatedly Reactive Screening Tests for Hepatitis C Virus; (2) Supplemental Testing, and the Notification of Consignees and Transfusion Recipients of Donor Test Results for Antibody to HCV (Anti-HCV), 6/17/99 [Replaces 9/23/99 Guidance]
- Guidance for Industry: Platelet Testing and Evaluation of Platelet Substitute Products. 5/20/99
- Guidance for Industry: Efficacy Studies to Support Marketing of Fibrin Sealant Products Manufactured for Commercial Use, 5/20/99
- Draft Guidance/Implementation for Industry: Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeld-Jakob Disease (CJD) and new variant Creutzfeld-Jakob Disease (nvCJD) by Blood and Blood Products, 8/99 [Final Guidance 11/23/99]
- Direct Final Rule and Companion Proposed Rule: Revisions to the Requirements Applicable to Blood, Blood Components and Source Plasma, 8/19/99
- Proposed Rule: Requirements for Testing Human Blood Donors of Evidence of Infection Due to Communicable Disease Agents, 8/19/99
- Proposed Rule: General Requirements for Blood, Blood Components and Blood Derivatives; Notification of Deferred Donors, 8/19/99
- Advanced Notice of Proposed Rulemaking: Plasma Derivatives and Other Blood-Derived Products; Requirements for Tracking and Notification, 8/19/99
- Draft Guidance for Industry: Application of Current Statutory Authority to Nucleic Acid Testing of Pooled Plasma, 11/26/99
- Database for Emerging Infectious Diseases, 4/99

- Workshop: Potential Transfusion Transmission of Tick Borne Agents, 1/14-15/99
- Workshop: Blood Donor Suitability Workshop: Donor History of Hepatitis, 7/21/99
- Workshop: International Workshop on Clearance of TSE Agents from Blood Products and Implanted Tissues, 9/13-14/99
- Workshop: Bacterial Contamination of Platelets, 9/24/99
- Workshop: Criteria for Safety and Efficacy Evaluation of Oxygen Therapeutics as Red Cell Substitutes, 9/27-28/99
- Workshop: Plasticizers: Scientific Issues in Blood Collection, Storage and Transfusion, 10/18/99
- Workshop: Standards for Inactivation and Clearance of Infectious Agents in the Manufacture of Plasma Derivatives from Non-Human Source Materials for Human Injectable Use, 10/25/99
- Open Public Meeting: Public Comment during the Comment Period of 4 recently Published Documents. ANPR-Tracking and Notification/DFR-Requirements for Blood/PR-Donor Notification/PR-Testing, 11/22/99
- Workshop: Blood Donor Suitability, 12/9/99
- Workshop: Universal Leukoreduction, 12/10/99
- Workshop: NAT Implementation, 12/14/99

FY00

- Draft Guidance to Industry: Changes to an Approves Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture 1/3/00
- Revision of Requirements Applicable to Albumin (Human), Plasma Protein Fraction (Human), and Immune Globulin (Human); Confirmation in Part and Technical Amendment; Final Rule - 3/14/00
- Final Guidance for Industry: Pilot Program: Gamma Irradiation, 3/15/00
- Final Guidance for Industry: Recognition and Use of a Standard for the Labeling of Blood and Blood Components, 6/6/00
- Draft Guidance: Pilot Program: CBER Pilot Licensing Program for Immunization of Source Plasma Donors with Immunogen Red Blood Cells Obtained from an Outside Supplier, (July 18, 2000)
- Revision or Requirements Applicable to Albumin (Human), Plasma Protein Fraction (Human), and Immune Globulin (Human), (August 28, 2000)
- Reporting Biological Product Deviations in Manufacturing, (November 7, 2000)
- Proposed Rule: Current Good Manufacturing Practices for Blood and Blood Components: Notification of Consignees and Transfusion Recipients

Receiving Blood and Blood Components at Increased Risks of Transmitting HCV Infection (Lookback), (November 16, 2000)

- Draft Guidance: Variances for Blood Collection from Individuals with Hereditary Hemochromatosis, December 20, 2000)
- Workshop: Donor Incentives, (February 28, 2000)
- Workshop: CDC- Public Meeting on Donor Suitability Standards (June 26-27, 2000)
- Workshop: Donor Recruitment Practices, (July 6-7, 2000)
- Workshop: TSE Diagnostics, (September 21-23, 2000)
- Workshop: Streamlining the Blood Donor Questionnaire, (September 29, 2000)

FY01

- Revisions to the Requirements Applicable to Blood, Blood Components, and Source Plasma; Conformation in Part and Technical Amendment, (January 10, 2001)
- Donor Incentives (Draft Compliance Policy Guide), (January 16,2001)
- Pre-Storage Leukocyte Reduction of Blood and Blood Components – Draft Revised Guidance, (January 23, 2001
- Final Rule: Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents, (June 11, 2001)
- Final Rule: General Requirements for Blood, Blood Components and Blood Derivatives; Notification of Deferred Donors, (June 11, 2001)
- Reporting Form and Database for Reporting Biological Product Deviation in Manufacturing (June 18, 2001)
- Final Guidance: Pilot Program: CBER Pilot Licensing Program for Immunization of Source Plasma Donors with Immunogen Red Blood Cell Obtained from an Outside Supplier, (July 11, 2001)
- Revisions to the Requirements Applicable to Blood, Blood Components, and Source Plasma, (August 6, 2001)
- Draft Guidance to Industry: Reporting Biological Product Deviation in Manufacturing (2 Guidance Documents), (August 11, 2001)
- Final Guidance: Variances for Blood Collection from Individuals with Hereditary Hemochromatosis, (August 22, 2001)

FY02

- Draft Guidance: Streamlining the Donor Interview Process: Recommendations for Self-Administered Questionnaires, (April 19, 2002)
- Final CPG: Donor Incentives, (May 17, 2002)

FY03

- Final Guidance: Streamlining the Donor Interview Process: Recommendations for Self-Administered Questionnaires, (July 7, 2003)
- Proposed Rule: Revisions to Labeling and Storage Requirements for Blood and Blood Components, Including Source Plasma, (July 29, 2003)
- Final Guidance: Notifying FDA of Fatalities Related to Blood Collection or Transfusion, (September 22, 2003)
- Final Guidance: An Acceptable Circular of Information for the Use of Human Blood and Blood Components (December 9, 2003)
- Proposed Rule: Revisions to Labeling and Storage Requirements for Blood and Blood Components, Including Source Plasma (July 30, 2003)

FY04

- Final Guidance: Use of Nucleic Acid Tests on Pooled and Individual Samples form Donors of Whole Blood and Blood Components (including Source Plasma and Source Leukocytes) to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV, (October 21, 2004)
- Workshop on Plasma Standards (August 31, 2004)
- Workshop on Use of Radiolabled Platelets for Assessment of In Vivo Viability of Platelet Products (May 3, 2004)

FY05

- Final Guidance: Assessing Donor Suitability and Blood and Blood Product Safety in Cases of Known or Suspected West Nile Virus Infection (June 23, 2005)
- Draft Guidance: Nucleic Acid Testing (NAT) for Human Immunodeficiency Virus Type 1 (HIV-1) and Hepatitis C Virus (HCV): Testing, Product Disposition, and Donor Deferral and Reentry (July 19, 2005)
- Workshop on Biological Therapeutics for Rare Plasma Protein Disorders (June 13, 2005)
- Workshop on Leukocyte Reduction of Blood and Blood Components (July 20, 2005)

FY06

- Final Guidance: Gamma Irradiation of Blood and Blood Components: A Pilot Program for Licensing; Withdrawal of Guidance (April 10, 2006)
- Draft Guidance: Pilot Program for Immunization of Source Plasma Donors Using Immunogen Red Blood Cells Obtained from an Outside Supplier; Withdrawal of Guidance (April 11, 2006)
- Draft Guidance" Amendment (Donor Deferral for Transfusion in France Since 1980) to "Guidance for Industry: Revised Preventive Measures to

Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CLD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products" (August 8, 2006)

- Final Guidance: Implementing a Collection Program for Source Plasma Containing Disease-Associated and Other Immunoglobulin (IgG) Antibodies (August 8, 2006)
- Final Guidance: Recognition and Use of a Standard for Uniform Blood and Blood Component Container Labels (September 22, 2006)
- Final Guidance: Biological Product Deviation Reporting for Blood and Plasma Establishments (October 18, 2006)
- Final Guidance: Implementation of Acceptable Full-Length Donor History Questionnaire and Accompanying Materials for Use in Screening Donors of Blood and Blood Components (October 27, 2006)
- Workshop on Behavior-Based Donor Deferrals in the NAT Era (March 8, 2006)
- Workshop on Testing for Malarial Infections in Blood Donors (July 12, 2006)

FY07

- Final Guidance: Informed Consent Recommendations for Source Plasma Donors Participating in Plasmapheresis and Immunization Programs, (June 20, 2007)
- Final Guidance: "Lookback" for Hepatitis C Virus (HCV): Product Quarantine, Consignee Notification, Further Testing, Product Disposition, and Notification of Transfusion Recipients Based on Donor Test Results Indicating Infection with HCV, (August 24, 2007)
- Final Guidance: Adequate and Appropriate Donor Screening Tests for Hepatitis B; Hepatitis B Surface Antigen (HBsAg) Assays Used to Test Donors of Whole Blood and Blood Components, Including Source Plasma and Source Leukocytes (November 21, 2007)
- Final Guidance: For Industry and FDA Review Staff; Collection of Platelets by Automated Methods (December 17, 2007)
- Final Rule: Current Good Manufacturing Practice for Blood and Blood Components; Notification of Consignees and Transfusion Recipients Receiving Blood and Blood Components at Increased Risk of Transmitting Hepatitis C Virus Infection (July 24, 2007)
- Direct Final Rule: Revisions to Requirements Applicable to Blood, Blood Components and Source Plasma (August 15, 2007)
- Proposed Rule: Requirements for Human Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use (November 8, 2007)
- Workshop on Licensure of Apheresis Blood Products (August 15, 2007)

- Final Guidance: For Industry and FDA Review Staff: Collection of Platelets by Automated Methods (December 17, 2007)

FY08

- Draft Guidance: Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Donors of Whole Blood and Blood Components Intended for Transfusion and Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), (April 25, 2008)
- Draft Guidance: Requalification Method for Reentry of Blood Donors Deferred Because of Reactive Test Results for Antibody to Hepatitis B Core Antigen (Anti-HBc), (May 20, 2008)
- Draft Guidance: Nucleic Acid Testing (NAT) to Reduce the Possible Risk of Parvovirus B19 Transmission by Plasma-Derived Products, (July 30, 2008)
- Workshop to Consider Approaches to Reduce the Risk of Transfusion-Transmitted Babesiosis in the United States (September 12, 2008)

APPENDIX 2: Office of the Secretary's Office of Public Health and Science Draft Strategic Plan

Draft Strategic Plan
Of The Office of Public Health and Science (OPHS)
2008-2012

Message From The Assistant Secretary for Health (ASH)

A good plan, and the process of creating it, enhances any organization's effectiveness. That is why, in early 2008, the Office of Public Health and Science (OPHS) set about to formulate a Strategic Plan (Plan). This Plan will enable OPHS to best serve the Secretary of the U.S. Department of Health and Human Services (HHS).

This Plan articulates the *Mission*, the *Vision*, and the *Values* of OPHS that support the achievement of three overarching OPHS *Goals*:

- *Prevention* - Prevent disease and improve the health of individuals and communities;
- *Disparities* - Reduce and, ultimately eliminate health disparities; and,
- *Public Health Infrastructure* - Promote effective, sustainable, and consistent public health systems.

As a framework for future OPHS activities, this Plan is specific enough to fit within the more expansive goals of the HHS Strategic Plan[1]. This framework also remains sufficiently broad that programs and activities of individual OPHS offices will fit within the structure.

This Plan also provides OPHS leadership, managers, and staff, other divisions in HHS, and the extensive public health community outside HHS a common snapshot of:

- Who we are;
- What we do; and,
- Why it's important.

As Assistant Secretary for Health, I believe that the OPHS Strategic Plan will foster communication, will illuminate shared values, and will define and direct collaborative activities between OPHS offices, between OPHS and other divisions of the Department of Health and Human Services (HHS), and between OPHS and external entities with a stake in the health of the Nation. This Plan is a framework that will help OPHS design effective, practical, and instructive programs to improve and enrich the health of the Nation. The Strategic Plan will bring our vision, *a Nation in which healthy people live in healthy communities, sustained by effective, efficient and coordinated public health systems*, significantly closer to reality.

[1] U.S. Department of Health and Human Services. U.S. Department of Health and Human Services Strategic Plan: Fiscal Years 2007-2012.

Draft Strategic Plan
Of The Office of Public Health and Science (OPHS)
2008-2012

Table 1. Components of the Office of Public Health and Science (OPHS)	
Component	**Acronym**
Blood Safety and Availability	BSA
National Vaccine Program Office	NVPO
Office of Commissioned Corps Force Management	OCCFM
Office of Disease Prevention and Health Promotion	ODPHP
Office of HIV/AIDS Policy	OHAP
Office for Human Research Protections	OHRP
Office of Minority Health	OMH
Office of Population Affairs	OPA
Office of Research Integrity	ORI
Office of the Surgeon General	OSG
Office on Women's Health	OWH
Presidential Advisory Council on HIV/AIDS	PACHA
President's Council on Bioethics	PCB
President's Council on Physical Fitness and Sports	PCPFS
Regional Health Administrators	RHAs

As a result, when an issue naturally cuts across HHS components (such as vaccines, blood safety, or special populations), OPHS coordinates with the relevant operating divisions the programs, research, and activities related to the issue. This collaboration achieves for the Nation:

- better use of resources by avoiding unnecessary duplication of effort;
- clarity in policies that helps ensure that the public receives consistent accurate information; and,
- high quality programs and activities through reliance on the wealth of knowledge and expertise in the HHS operating divisions.

Draft Strategic Plan
Of The Office of Public Health and Science (OPHS)
2008-2012

Mission, Vision, and Values of OPHS

Mission

The mission of the Office of Public Health and Science (OPHS) is to protect and promote the public health of the Nation through policies and programs that apply science-based approaches that enable people to live healthier lives.

Vision

The OPHS sees a Nation in which healthy people live in healthy communities, sustained by effective, efficient and coordinated public health systems.

Values

Put People First

- Honor the public's trust and confidence;
- Respect for colleagues and the public health professions; and,
- Recognize the invaluable contributions of OPHS staff.

Integrity

- Adhere to the highest ethical standards;
- Ensure products and services are truthful, accurate, and comprehensive;
- Assure health research conforms to scientific norms; and,
- Recognize that privacy and safety of human participants is paramount.

Excellence

- Conduct programs and activities guided by science and driven by results;
- Delineate clear and enforce consistent accountability for program outcomes;
- Design programs and activities so that rigorous program evaluations can and will be performed; and,
- Promote public health that is effective, efficient, and community-delivered.

Draft Strategic Plan
Of The Office of Public Health and Science (OPHS)
2008-2012

Diversity

- Embrace the richness of OPHS' diversity and seek to strengthen it;
- Value the diversity of our Nation and the perspectives brought by differences in race, ethnicity, gender, age, and socio-economic status; and,
- Believe that all Americans should benefit from advances in health promotion.

Leadership Through Collaboration

- Commit to disease prevention and health promotion;
- Believe that collaboration and coordination builds effective, efficient, responsive, and sustainable public health systems; and,
- Foster input from all relevant partners and stakeholders in program operations.

Draft Strategic Plan
Of The Office of Public Health and Science (OPHS)
2008-2012

OPHS Goals, Objectives, and Strategies

The Office of Public Health and Science (OPHS) will use this strategic plan as a framework for accomplishing its vision: *a Nation in which healthy people live in healthy communities, sustained by effective, efficient and coordinated public health systems.* This vision is the target outcome for current and future OPHS activities. The values and mission statement establish the direction of OPHS activities toward achievement of the vision. Similarly, the following three goals and associated objectives and strategies are the methods to reach the vision. Over the next four years, OPHS leadership will concentrate resources and management efforts on achieving these goals:

- *Goal 1: Prevent disease and improve the health of individuals and communities.* {Alignment: HHS Strategic Plan Objective 2.3}[5]

- *Goal 2: Reduce, and ultimately, eliminate health disparities.* {Alignment: HHS Strategic Plan Objective 3.4}[6]

- *Goal 3: Promote effective, sustainable, and consistent public health systems.* {Alignment: HHS Strategic Goal 4}[7]

Associated with each of the three goals are five objectives:

- *Objective A: Shape public health policy at the local, state, national, and international levels;*
- *Objective B: Communicate strategically;*
- *Objective C: Promote effective partnerships;*
- *Objective D: Build a stronger science base; and,*
  Objective E: Lead and coordinate key initiatives of HHS and Federal health initiatives.

Finally, specific strategies associated with each goal and each objective further define the actions OPHS will take today and in the future to ultimately reach the vision. The three goals will be achieved through implementation of the explicit strategies which follow.

Goal 1: Prevent disease and improve the health of individuals and communities

[5] HHS Strategic Plan Objective 2.3: Promote and encourage preventive health care, including mental health, lifelong healthy behaviors, and recovery.
[6] HHS Strategic Plan Objective 3.4: Address the needs, strengths, and abilities of vulnerable populations.
[7] HHS Strategic Plan Objective 4: Advance scientific and biomedical research and development related to health and human services.

Draft Strategic Plan
Of The Office of Public Health and Science (OPHS)
2008-2012

Objective A: Shape public health policy at the local, state, national, and international levels

Strategy 1.A.1: Lead the development and oversight of Healthy People 2020 for the Nation.

Strategy 1.A.2: Lead the development and monitoring of the *National Vaccine Plan* to ensure coordination of the various components of the Nation's vaccine system in order to achieve optimal prevention of human infectious diseases through immunization.

Strategy 1.A.3: Lead the HHS reproductive health programs that reduce unintended pregnancies, adolescent pregnancies, and the transmission of sexually transmitted diseases by developing and implementing policies and programs related to family planning and other preventive healthcare services, including education and social support services.

Objective B: Communicate strategically

Strategy 1.B.1: Ensure that *healthfinder.gov* becomes the pre-eminent federal gateway for up-to-date, reliable, evidence-based prevention information so that individuals are empowered to adopt healthy behaviors.

Strategy 1.B.2: Maximize the number of Americans who know their HIV health status through targeted HIV awareness and testing campaigns.

Strategy 1.B.3: Emphasize effectively with federal, state, and local stakeholders the extensive systems changes needed in school nutrition and physical activity programs, community infrastructure, and nutrition programs for the poor to reduce childhood obesity.

Strategy 1.B.4: Advance programs and activities that improve health literacy through provision of evidence-based and culturally competent health care.

Objective C: Promote effective partnerships

Strategy 1.C.1: Use the *Healthy People Consortium* to make Americans healthier by encouraging use of *Healthy People 2020* objectives at national, state, and local levels.

Strategy 1.C.2: Partner with national public health organizations and medical associations to identify emerging public health and science issues, disseminate

information on key initiatives and priorities, and leverage existing programs in order to maximize the positive impact on the nation's health.

Strategy 1.C.3: Through a variety of collaborations, drive community-led discussions about HIV-related stigma and risk behaviors to strengthen HIV/AIDS prevention efforts.

Objective D: Build a stronger science base

Strategy 1.D.1: Lead the development, promotion, and evaluation of evidence-based *Physical Activity Guidelines* for the Nation to help Americans achieve appropriate levels of physical activity that lead to good health.

Strategy 1.D.2: Lead, with the United States Department of Agriculture, the development, promotion, and evaluation of evidence-based *Dietary Activity Guidelines* for the Nation to help Americans eat a nutritionally balanced diet.

Strategy 1.D.3: Develop and promote future *Surgeon General's Calls to Action* such as those on the prevention of deep venous thrombosis (DVT), on the prevention and reduction of underage drinking, on improvement of the health and wellness of persons with disabilities, on the promotion of oral health, and on the prevention and reduction of overweight and obesity.

Objective E: Lead and coordinate key initiatives of HHS and Federal health initiatives

Strategy 1.E.1: Lead the department in its effort to improve vaccine safety and public confidence in vaccines in order to maintain high national immunization rates.

Strategy 1.E.2: Develop and implement a HHS plan to reduce healthcare associated infections (HAI) that includes prioritizing recommended clinical practices, strengthening data systems, and developing and launching a national HAI prevention campaign.

Strategy 1.E.3: Lead the Federal initiative, *Healthy Youth for a Healthy Future*, to prevent childhood overweight and obesity, by partnering with communities throughout the Nation that are helping kids stay active, encouraging healthy eating habits, and promoting healthy choices.

Strategy 1.E.4: Lead the *President's Council on Physical Fitness & Sports (PCPFS)* in efforts to significantly increase physical activity in this country.

Strategy 1.E.5: Continue OPHS' historic leadership to prevent and treat tobacco abuse and dependence.

Goal 2: Reduce, and ultimately, eliminate health disparities

Objective A: Shape public health policy at the local, state, national, and international levels

Strategy 2.A.1: Provide leadership across the Nation to guide, organize, and coordinate the systemic planning, implementation, and evaluation of policies and programs designed to achieve targeted results relative to minority health and health disparities reduction.

Strategy 2.A.2: Provide leadership to promote health equity for women and girls through the development of innovative programs, through the education of health professionals, and through the motivation of consumer behavior change by disseminating relevant health information.

Strategy 2.A.3.: Expand Commissioned Corps initiatives to recruit and retain officers in assignments that meet the public health needs of underserved populations.

Objective B: Communicate strategically

Strategy 2.B.1: Ensure that the *Office on Women's Health Resource Center* and the *Office of Minority Health Resource Center* become the nation's pre-eminent gateways for women's health and minority health information.

Strategy 2.B.2: Significantly increase the number of health care professionals using the nationally accredited on-line *Cultural Competency Training* modules to increase their knowledge and skills to better treat the increasingly diverse U.S. population.

Strategy 2.B.3: Advocate for widespread access for health care providers to foreign language resources to improve communications with patients and families with limited English proficiency (LEP).

Objective C: Promote effective partnerships

Strategy 2.C.1: Ensure that the *National Partnership for Action to End Health Disparities* connects and mobilizes organizations throughout the Nation to build a renewed sense of teamwork across communities, share success stories for replication, and create methods and tactics to support more effective and efficient actions.

Strategy 2.C.2: Through the *Leadership Campaign on AIDS*, provide technical assistance to minority communities so that they are at the forefront in the fight against HIV/AIDS.

Objective D: Build a stronger science base

Strategy: 2.D.1: Develop and test interventions designed to address racial and ethnic disparities through community-level activities that promote health, reduce risks, and increase access to and utilization of appropriate preventive healthcare and treatment services.

Strategy 2.D.2: Foster the development of evidence-based health and disease prevention practices for women through innovative national and community-based programs focused on conditions affecting women's health.

Objective E: Lead and coordinate key initiatives of HHS and Federal Health Initiatives

Strategy 2.E.1: Ensure that the distinctive cultural, language, and health literacy characteristics of minority and special needs populations are integrated into all-hazards emergency preparedness plans.

Strategy 2.E.2: Provide leadership and oversight for the *Minority AIDS Initiative* to ensure that departmental efforts strengthen the organizational capacity of community-based providers and expand HIV-related services for racial and ethnic minority communities disproportionately affected by HIV/AIDS.

Strategy 2.E.3: Lead and manage the *HHS American Indian Alaska Native Health (AI/AN) Research Advisory Council* to ensure input from tribal leaders on health research priorities, to provide a forum through which HHS can better coordinate its AI/AN research, and to establish a conduit for improved dissemination of research to tribes.

Strategy 2.E.4: Lead and manage the *HHS Work Group on Asian, Native Hawaiian and Other Pacific Islander issues* to provide a forum for HHS to develop strategies for improving the health of these communities.

Goal 3: Strengthen the Public Health Infrastructure

Objective A: Shape public health policy at the local, state, national, and international levels

Strategy 3.A.1: Promote emergency preparedness by strengthening the capacity and capability of Medical Reserve Corps (MRC) units in local communities across the country.

Strategy 3.A.2: Provide advice and consultation to the Executive Branch on ethical issues in health, science, and medicine.

Strategy 3.A.3: Lead the development of national blood, tissue, and organ donation policy to maintain and enhance safety through prevention of disease transmission and other adverse events during transfusion and transplantation.

Strategy 3.A.4: Strengthen the public health mission of the Public Health Service Commissioned Corps through research, applied public health, and provision of health care services including behavioral and mental health.

Objective B: Communicate strategically

Strategy 3.B.1: Foster effective communication to the public that promotes and increases blood and organ donation.

Strategy 3.B.2: For people with multiple chronic conditions, advocate for changes in the research, clinical, health professional education, financing, and health delivery enterprises so that their health can be better managed and acute exacerbations of conditions can be prevented.

Objective C: Promote effective partnerships

Strategy 3.C.1: Expand memorandums of understanding (MOUs) and memorandums of agreement (MOAs) between the Commissioned Corps and local, state, and federal health agencies to allow placement of officers in other government organizations (outside HHS).

Strategy 3.C.2: Support Commissioned Corps initiatives to recruit, develop, and retain a competent health care workforce.

Objective D: Build a stronger science base

Strategy 3.D.1: Educate the broad research community on federal regulations that protect human subjects in research.

Strategy 3.D.2: Educate the broad research community on research integrity to minimize cases of research misconduct and to decrease the number of misconduct cases that go unreported.

Strategy 3.D.3: Ensure that Public Health Reports remains a pre-eminent peer-reviewed journal on public health practice and public health research for healthcare professionals.

Objective E: Lead and coordinate key initiatives of HHS and Federal health initiatives

Strategy 3.E.1: Lead the transformation of the Commissioned Corps into a mobile, organized, ready, and responsive force that ensures the preparedness of the Nation for emergency response.

Strategy 3.E.2: Engage the Commissioned Corps in health diplomacy missions to provide critically needed medical and public health services beyond our borders.

Strategy 3.E.3: Support the Regional Health Administrators as key coordinators of prevention and preparedness activities at the local, state, and regional level.

Strategy 3.E.4: Lead HHS initiatives to enhance transfusion and transplantation safety and to improve blood availability through collaboration and coordination with relevant stakeholders internal and external to HHS.

Conclusion

The Nation's public health system has continually evolved over the past century to meet existing and emerging challenges. As a result of this dynamic system, many Americans are living longer, healthier, and fuller lives. In fact, during the 20th century, the average life expectancy increased by nearly 30 years.

Undoubtedly, the Nation's public health system will endure trials and celebrate success over the coming years. To anticipate future threats and effectively meet today's challenges, the OPHS coordinates across HHS divisions. As a result, HHS is better able to align policies and programs to ensure federal, state, tribal, and local health agencies have the infrastructure in place to provide essential public health services.

The success of the public health system cannot be measured by OPHS's or HHS's efforts alone. Rather, success will be directly dependent on the creation of effective partnerships across government, states, communities, and other private and public organizations to help build and sustain capacity to protect and promote the health of all Americans. The Office of Public Health and Science is leading this charge and looks forward to a future of healthy individuals living in healthy communities.

Draft Strategic Plan
Of The Office of Public Health and Science (OPHS)
2008-2012

Appendix A

Organization of the Office of Public Health and Science

The Office of Public Health and Science (OPHS) conducts its public health, advisory, and coordination activities through 13 organizational components, 10 regional offices, and the U.S. Public Health Service (PHS) Commissioned Corps (the Corps). The Assistant Secretary for Health (ASH) is the primary advisor to the HHS Secretary on public health and science policy for the Nation. As such, the ASH, through OPHS, guides HHS on prevention and population-based public health services, directs organizational components housing essential public health activities, and provides senior leadership across HHS on Secretarial initiatives.

A key component of the ASH's advisory role is identification and anticipation of emerging public health issues to ensure HHS reacts appropriately to today's and tomorrow's health challenges. While OPHS does not typically implement the HHS plans that address these burgeoning concerns, OPHS leads the HHS response to these situations by:

- defining the relevant issues;
- identifying and leveraging resources;
- coordinating the development of the HHS plan for addressing the matter;
- solving problems and resolving conflicts; and,
- monitoring progress in achieving goals.

As a result, the relevant HHS operating divisions[8] are able to focus on the effective application of their substantial program resources and considerable expertise in implementing the HHS plan to mitigate the challenge to public health.

The ASH also is responsible for oversight of and policy development for the Commissioned Corps, an elite force of more than 6,000 well-trained, highly qualified public health professionals[9] dedicated to protecting, promoting, and advancing the health and safety of the Nation. Likewise, the Surgeon General (SG) implements Corps policy and manages operations of the Corps including training and assignment of officers, deployment of special response teams to public health emergencies, and allocation of officers to underserved

[8] The HHS operating divisions include: the Administration for Children and Families (ACF); the Administration on Aging (AoA); the Centers for Medicare & Medicaid Services (CMS); the Agency for Healthcare Research and Quality (AHRQ); the Centers for Disease Control and Prevention (CDC); the Agency for Toxic Substances and Disease Registry (ATSDR); the Food and Drug Administration (FDA); the Health Resources and Services Administration (HRSA); the Indian Health Service (IHS); the National Institutes of Health(NIH); the Office of the Inspector General (OIG); and, the Substance Abuse and Mental Health Services Administration (SAMHSA).

[9] The types of health professionals serving in the Commissioned Corps include (but may not be limited to): physicians; dentists; registered nurses; pharmacists; veterinarians; environmental health specialists; allied health professionals; health services professionals; mental health specialists; emergency responders; and, social workers.

communities and populations. Moreover, Commissioned Corps officers assist the ASH in carrying out the OPHS mission in almost every office in HHS and fill essential public health leadership and service roles within the Nation's other Federal agencies and programs.

Within each of 10 regional offices, a Regional Health Administrator (RHA) from OPHS advances prevention and preparedness and coordinates regional activities across HHS agencies. The RHAs manage portfolios of funds and staff to further the goals of OPHS. Moreover, in partnership with the Regional Emergency Coordinators (RECs) of the Office of the Assistant Secretary for Preparedness and Response (OASPR), with other Federal agencies, and with State and local leaders, the RHAs are prepared to respond to all public health hazards. The RHAs maintain this all-hazards preparedness by up-to-date training in emergency response. The RHAs also act as the conduit for sharing information on public health issues between HHS and State and local representatives in the ten regions.

Draft Strategic Plan
Of The Office of Public Health and Science (OPHS)
2008-2012

Appendix B

The Office of Public Health and Science in Action

While the Office of Public Health and Science (OPHS) components are diverse in nature and focus, they work in partnership with each other and with other HHS divisions to form a proficient and capable Federal public health system. Recent OPHS contributions are:

- *Shape public health policy at the local, state, national, and international levels*

  Highlights:

  - The HHS *Pandemic Influenza Plan* provides the blueprint for local, state, national, and international pandemic influenza preparedness.
  - The Surgeon General's report, *The Health Consequences of Involuntary Exposure to Tobacco Smoke*, was the primary catalyst for at least 12 nations, 26 States, 42 of the 50 largest U.S. cities[10], and hundreds of smaller communities to pass ordinances and laws protecting their citizens in workplaces and public places from the threats of second-hand smoke.

- *Communicate strategically*

  Highlights:

  - Over 11 million people use *Healthfinder*, OPHS' award-winning, multi-lingual web portal for reliable consumer health information.
  - Over five million people use *The Presidents Challenge Program* which provides messages, tools, and resources to help Americans increase physical activity.
  - During *National Women's Health Week*, nearly 45,000 women and girls in over 300 communities learn, foster, and celebrate healthy lifestyle practices that will help them live longer, fuller lives.

10 These numbers are totals as of July 2008 and may change over time.

- *Promote effective partnerships*

  Highlights:

  - OPHS coordinates the Medical Reserve Corps (MRC), teams of volunteer medical and public health professionals at the local level who contribute skills and expertise throughout the year and during times of great need. Over 150,000 volunteers serve in more than 700 Medical Reserve Corps (MRC) units across the country.

  - The *National Partnership for Action* is creating a Nation free of racial and ethnic health disparities through OPHS' collaborations with over 25 national organizations, state-based partners in 46 states, nearly 25 community partnership programs, and the nation's only non-profit, membership organization of more than 300 "Fortune 500" and other large companies.

  - It is estimated that nearly one million unintended pregnancies are averted annually through the provision of Title X Family Planning Services by OPHS grantees.

- *Build a stronger science base*

  Highlights:

  - In 2007, more than 1,550 persons completed the "Responsible Conduct of Research Training" course developed by the Office of Research Integrity in partnership with the *Collaborative Institutional Training Initiative.*

  - In 2007, the Office for Human Research Protections provided education via sponsored conferences and/or quality assurance workshops to over 1350 persons involved in human research programs.

- *Lead and coordinate key initiatives of HHS*

  Highlights:

  - Sixty percent of *Healthy People 2010 (HP2010)* objectives have met their target or are moving in the right direction and 46 States have used HP2010 to develop state health plans[11].

  - OPHS chairs the HHS *Minority AIDS Initiative (MAI) Steering Committee on Implementation and Evaluation* to help oversee the disbursement of $50 million across HHS operating and staff divisions for the identification of HIV-related best practices.

  - OPHS leads a Secretarial Prevention Initiative which has received over $327 million in donated media support, a quantifiable index for measuring a campaign's success. The Initiative includes the *HHS Childhood Obesity and Overweight Prevention Council.*

- *Coordinate Federal health efforts that bridge departments*

  Highlights:

  - OPHS coordinates *The HealthierUS Initiative* across 12 Federal departments (including HHS)[12]. The Initiative encourages Americans to live healthier lives by emphasizing improved nutrition, increased physical activity, preventive screenings, and reduction of risk-taking behaviors.

  - OPHS coordinates HealthierFeds through a joint partnership of the President's Council on Physical Fitness and Sports (PCPFS) with the Office of Personnel Management (OPM). Close to 40,000 Federal employees, retirees, contractors, and family member participated in the Physical Activity Challenge in 2007, which was offered to all three branches of the Federal government.

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[11] Numbers reflect totals as of July 2008. Totals may change over time.
[12] The Federal agencies participating in "The HealthierUS Initiative" are: the Departments of Agriculture (USDA), Defense (DoD), Education (DoE), Health and Human Services (HHS), Housing and Urban Development (HUD), Interior (DoI), Labor (DoL), Transportation (DoT), and Veterans Affairs (VA); the Army Corps of Engineers (ACE); the Environmental Protection Agency (EPA); and, the General Services Administration (GSA).

- OPHS published the "*U.S. Dietary Guidelines for Americans*" jointly with the U.S. Department of Agriculture in 2005.

- In 2008, the Public Health Service Commissioned Corps increased its active duty force strength to the greatest number of officers in 10 years due to the recruitment and retention activities of the Commissioned Corps Transformation Initiative, headed by OPHS.

- During the devastating hurricanes of 2005, over 2,700 Public Health Service Commissioned Corps officers supported the Federal recovery efforts by:
  - triaging tens of thousands of people during evacuation;
  - vaccinating over 250,000 people;
  - re-establishing waste water systems across the Gulf Coast;
  - protecting the mental health of 200,000 school children;
  - treating over 6,000 animals in distress; and,
  - monitoring the disease status of millions.

APPENDIX 3: Tissue Transplant Record (Northwest Tissue Services)

NORTHWEST

TISSUE CENTER

TRANSPLANT INFORMATION RECORD

Please complete this form at the time of surgery for corresponding graft (whether transplanted or discarded). Return it to the Northwest Tissue Center in the envelope provided. The detachable labels are for your records. Please provide all requested information as this supplies important Donor Tissue data.

PLEASE PRINT ☐ Transplanted ☐ Discarded Date graft used _____

Transplant Facility Name _____

Address _____

City _____ State _____ Zip Code _____

Surgeon _____ Last _____ First _____ MI _____

Office Telephone ( ) _____

Name of Recipient _____ Last _____ First _____ MI _____

Medical Record # _____

Date of Birth ___/___/___ Sex ☐ F ☐ M

SAMPLE

PLEASE COMPLETE REVERSE SIDE AND CHECK BELOW

Reason for Surgery ☐ Tumor ☐ Trauma ☐ Degeneration ☐ Congenital ☐ Infection ☐ Osteoporosis ☐ Non-union ☐ Other _____

Graft Quality ☐ Excellent ☐ Good ☐ Fair ☐ Poor

Comments about the graft (i.e., handling, shape, size, packaging, service, etc.) _____

Form completed by _____ Title _____
(Print name)

Phone number _____ Date _____

02491 407 DONOR DEPOSITP

FCW10 FEM CNDYLE WHOLE F

NTC26127 ORDER NUMBER

These detachable labels are for transplant facility use to packing tissue (e.g., chart log, patient chart).
Please return transplant record to NTC.

FEM CNDYLE WHOLE F
ID#: 02491 407 FCW10
Exp. Date: 09/01/2005
NTC26127
Northwest Tissue Center
(800) 858-2262

FEM CNDYLE WHOLE F
02491 407 FCW10
Exp. Date: 09/01/2005
NTC26127
Northwest Tissue Center
(800) 858-2262

FEM CNDYLE WHOLE F
02491 407 FCW10
Exp. Date: 09/01/2005
NTC26127
Northwest Tissue Center
(800) 858-2262

FEM CNDYLE WHOLE F
ID#: 02491 407 FCW10
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(800) 858-2262

FEM CNDYLE WHOLE F
02491 407 FCW10
Exp. Date: 09/01/2005
NTC26127
Northwest Tissue Center
(800) 858-2262

FEM CNDYLE WHOLE F
02491 407 FCW10
Exp. Date: 09/01/2005
NTC26127
Northwest Tissue Center
(800) 858-2262

200-10 Rev. 5-98

APPENDIX 4: NMDP Form 701

National Marrow Donor Program®
Stem Cell Donor Adverse Event Form

Registry Use Only

Sequence Number:

Date Received:

Donor NMDP ID:

Recipient NMDP ID:

DC Code: TC Code:

AC Code: CC Code:

Today's Date: (Date form is completed) Month Day 2 0 Year

Date of Collection: (if applicable) Month Day 2 0 Year

Product type: (if applicable) ☐ Marrow ☐ PBSC ☐ Other, specify: _____

1. Is this the first Form 701 completed for this adverse event?
   1 ☐ yes, initial report
   2 ☐ no, follow-up report

2. Is this adverse event a serious adverse event?

A serious adverse event is defined as any event that results in any of the outcomes listed in question 3. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based on appropriate medical judgement, they may jeopardize the subject and/or may require intervention to prevent one of the outcomes listed in this definition.

   1 ☐ yes →
   2 ☐ no

3. Specify serious event outcome:
   1 ☐ death
   2 ☐ life-threatening event (results in an immediate risk of death from the reaction as it occurred)
   3 ☐ inpatient hospitalization or prolongation of existing hospitalization
   4 ☐ persistent or significant disability / incapacity
   5 ☐ congenital anomaly / birth defect
   6 ☐ other, specify: _____

4. Date of event onset: Month Day 2 0 Year

5. Describe the adverse event in detail:

If not using the NMDP FormsNet™ application, a copy of this completed form should be faxed to the NMDP Registry at 612/627-5893. Retain original at the Donor Center.

NMDP Form 0701 v2.0 (1-2) May 2008
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For internal use only. Document F0701 version 2.0 | Registry Document F-017 version 1.0 November 2008

APPENDIX 5: NMDP Form 760

National Marrow Donor Program®
Post-Donation – One Month, Six Months and Annual Donor Assessment

Registry Use Only

Sequence Number:

Date Received:

Donor NMDP ID:

Recipient NMDP ID:

DC Code: TC Code:

Today's Date: (Date form is completed) Month Day 2 0 Year

Date of Collection: Month Day Year ☐ n/a; filgrastim injection only

Date of Medical Evaluation from Form 700: Month Day Year

Followup visit for which this form is being completed: ☐ One Month (form 760) ☐ Six Months (form 761) ☐ Annual, specify which yearly visit number: (#1, #2, etc.) (form 762)

1. Date of actual contact with the donor: Month Day 2 0 Year

Conditions Present on Day of Contact

2. Using the following Modified Toxicity Criteria, review each body symptom with the donor. For each symptom associated with a system, select the statement that most closely reflects the donor's current condition.

In the Modified Toxicity Criteria below, the term "activities of daily living" (ADL) refers to tasks performed by individuals in a typical day that allow independent living. Basic activities of daily living include feeding, dressing, hygiene, and physical mobility.

Contact the NMDP Search Coordinating Unit to report any toxicities that are grade 3 or higher, and complete a Stem Cell Donor Adverse Event form.

FLU-LIKE SYMPTOMS

a. **Fever in absence of infections**
- 1 ☐ none (grade 0)
- 2 ☐ 38.0 – 39.0° C / 100.0 – 102.2° F (grade 1)
- 3 ☐ > 39.0 – 40.0° C / 102.2 – 104.0° F (grade 2)
- 4 ☐ > 40.0° C / 104.0° F for less than 24 hours (grade 3)
- 5 ☐ > 40.0° C / 104.0° F for more than 24 hours (grade 4)

CONSTITUTIONAL SYMPTOMS

b. **Fatigue (lethargy, malaise, asthenia)**
- 1 ☐ none (grade 0)
- 2 ☐ mild fatigue over baseline (grade 1)
- 3 ☐ moderate or causing difficulty performing some ADL (grade 2)
- 4 ☐ severe fatigue interfering with ADL (grade 3)
- 5 ☐ disabling (grade 4)

DERMATOLOGIC

c. **Skin (rash)**
- 1 ☐ none (grade 0)
- 2 ☐ macular or papular eruption or erythema that is asymptomatic (grade 1)
- 3 ☐ macular or papular eruption or erythema with pruritus or other associated symptoms (grade 2)
- 4 ☐ severe, generalized erythroderma or macular, papular or vesicular eruption (grade 3)
- 5 ☐ generalized exfoliative dermatitis or ulcerating dermatitis (grade 4)

d. **Local (site reaction), specify site:** _____
- 1 ☐ none (grade 0)
- 2 ☐ pain; itching; erythema (grade 1)
- 3 ☐ pain and swelling with inflammation or phlebitis (grade 2)
- 4 ☐ ulceration or necrosis that is severe; operative intervention indicated (grade 3)

If not using the NMDP FormsNet™ application, a copy of this completed form may be mailed to:
The NMDP Registry
Suite 500
3001 Broadway St. N.E.
Minneapolis, MN 55413
Retain original at the Donor Center.

NMDP Form 0760 v2.0 (1-4) May 2005
Copyright © 2005 National Marrow Donor Program. All rights reserved.
For internal use only. Document ID: [illegible] (version 2.0) [illegible] (PQI72-1.0 November [illegible])

APPENDIX 6: Cell Therapy Adverse Event Form (University of California San Diego Medical Center)

SCPL

Stem Cell Processing Laboratory
UCSDMC Thornton Hospital
La Jolla CA
Thomas A. Lane MD, Medical Director
858.657.6057

Recipient:
MRN:
DOB:

Adverse Event Report

Infusion Date: _____
Type of Product: _____

ALN#(s) Involved: _____

❑ Infusion reaction, expected*:
- ❑ Chills at time of infusion
- ❑ Fever ≤ 103° F (within 24 hours of infusion)
- ❑ Mild rigors
- ❑ Headache
- ❑ Nausea blood pressure +/- 30%
- ❑ Vomiting
- ❑ Other, specify: _____

❑ Infusion reaction, unexpected*:
- ❑ Fever > 103° F (within 24 hours of infusion)
- ❑ Hives
- ❑ Tachycardia
- ❑ Severe rigors
- ❑ Chest tightness/pain
- ❑ Other, specify: _____

❑ Positive Infectious Disease Marker, confirmed: Attach copy of testing

❑ Failure to engraft: Attach Copy of Engraftment Summary

❑ Other product failure, specify*: _____

*Attach supporting documentation as needed.

Reported By: _____ Date: _____
Facility: _____
Address: _____

Complete and return to the Stem Cell Processing Laboratory (MC 7767) at the address listed above

This section to be completed by SCPL Medical/Laboratory Director

Was the event fatal or life-threatening? ❑ Yes ❑ No
Did the event require surgical or medical intervention, including hospitalization? ❑ Yes ❑ No
Did the event result in permanent impairment of a body function or permanent damage to body structure? ❑ Yes ❑ No
Was the adverse event a direct result of the infusion of the stem cell product? ❑ Yes ❑ No
FDA Reportable? ❑ Yes ❑ No
Evaluation: _____

SCPL Medical/Laboratory Director Review: _____ Date: _____

AR Tracking Number: _____
Copy sent to attending physician: _____ Date: _____

Adverse Event Report (08/26/2005)

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