The Evolution of Blood Safety Mitigation Measures

IPFA 2016, Lisbon

Adonis Stassinopoulos, Ph.D
VP Global Scientific Affairs and Research

CERUS

Outline

- Unsustainability of Testing as the main method of protection against new pathogens
- PI *vs.* NAT
- Introduction to INTERCEPT 10+ year experience
- Applications of PI in residual safety and new safety issues
  - Bacteria
  - Emerging Pathogens

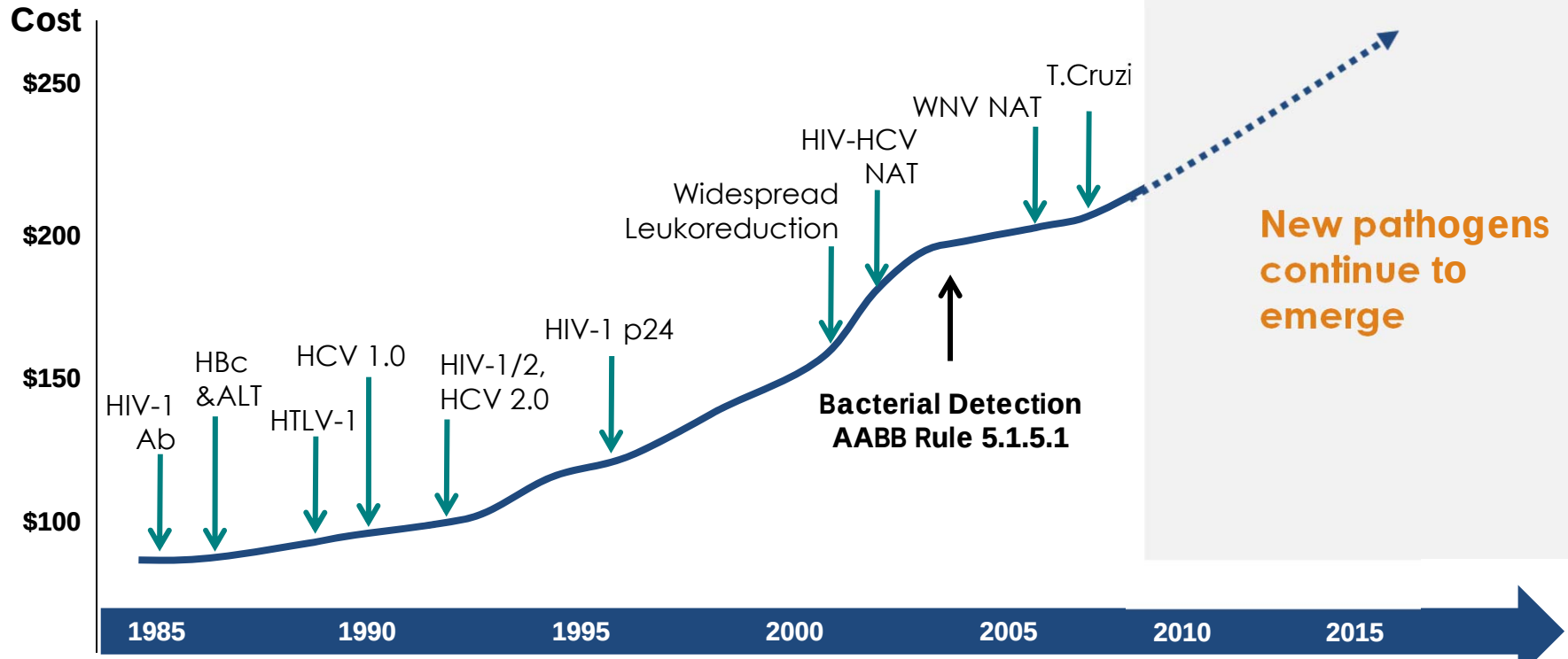
Conclusions

Emerging Pathogens: Is testing a sustainable solution?

Development time, cost, continual addition of new pathogens

25 years of testing = protection against 9 agents

HIV, Hepatitis B, Hepatitis C, HTLV, bacteria, West Nile virus, T. Cruzi, Syphilis,, Leukocytes



RBC price data adapted from B Custer & JS Hoch, *Transfusion Medicine Reviews*, 23, No 1 (January), 2009: pp 1-12

2003 **Pathogen Inactivation**

Pathogen Inactivation *vs.* Testing

Pathogen Inactivation

- One intervention per blood product
- Proactive
- Does not require prior knowledge of the pathogen, or additional development time
- If properly designed, ensures robust, broad inactivation
- Simpler business model

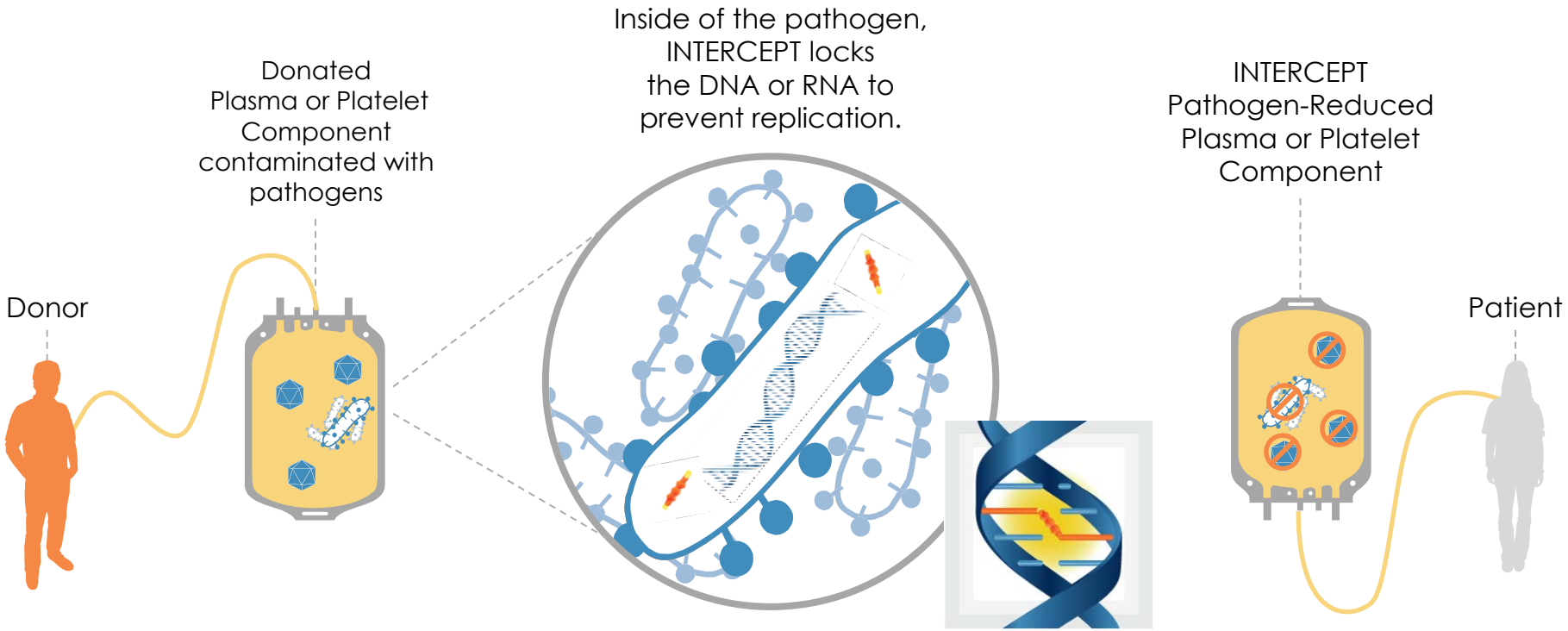
Nucleic Acid, or Ab Testing

- Developed per pathogen, and can be bundled, i.e. triplex vs. singlex
- Reactive
- Requires development and validation for sensitivity and specificity with characterized samples
- Sometimes needs to be used in addition to orthogonal assays, ie Ab and NAT
- Business model required for each pathogen

CERUS

INTERCEPT Blood System

Pathogen Reduction System



Donated plasma or platelet component(s) may contain harmful agents such as bacteria, viruses, protozoans, and/or white blood cells.

When pathogens are unable to replicate, they are considered "inactivated" and cannot infect patients.

Pathogen-reduced component can then be transfused into the patient

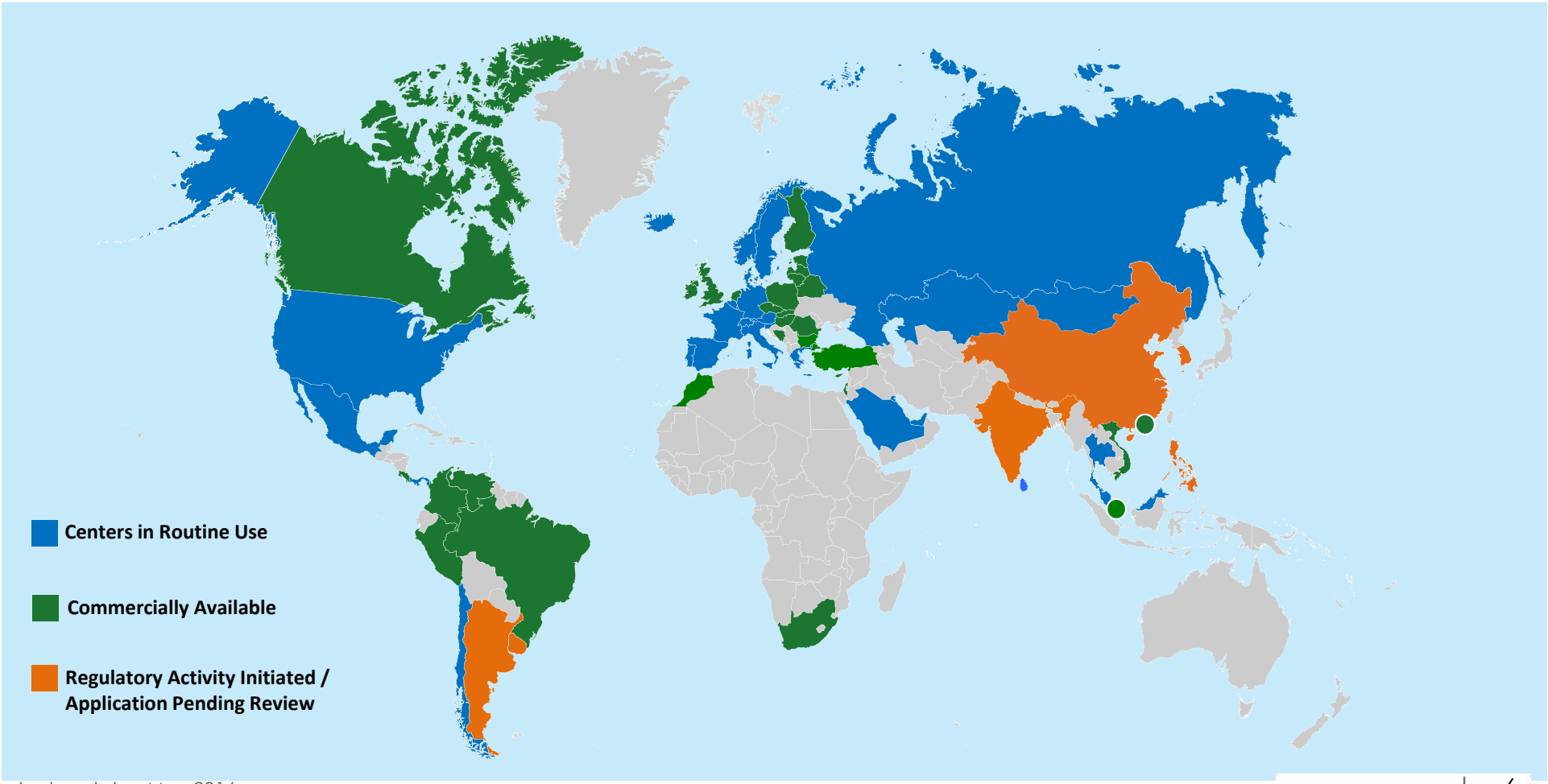
[1]INTERCEPT Blood System for Platelets [Package Insert]. Concord, CA: Cerus Corporation; 2016.
[2]INTERCEPT Blood System for Plasma [Package Insert]. Concord, CA: Cerus Corporation; 2015.

INTERCEPT BLOOD SYSTEM
PATHOGEN REDUCTION SYSTEM

MKT-EN 00156 v4

10+ Years of Routine Global Use

>100 Blood Centers in 25 Countries with kits sold to produce over 3,500,000 INTERCEPT platelet and plasma units

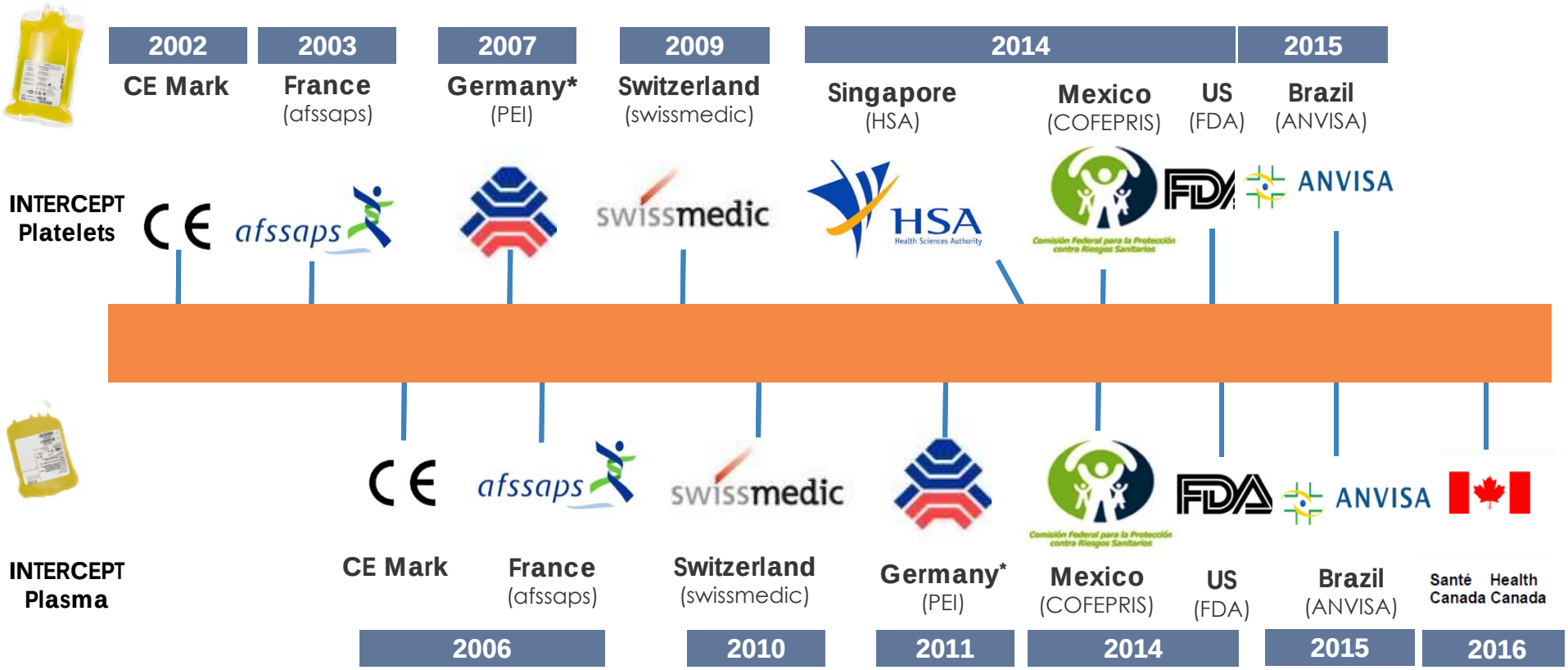


Last update: May 2016

INTERCEPT BLOOD SYSTEM
PATHOGEN REDUCTION SYSTEM

Select Regulatory Approvals

Status as of May 2016



Approvals shown do not represent a comprehensive list

* For first center approval

INTERCEPT BLOOD SYSTEM
PATHOGEN REDUCTION SYSTEM

Approved Claims by Reg. Authorities

- Use of INTERCEPT platelets and plasma without patient population exclusions
- Replacement of gamma irradiation for the prevention of TA-GvHD
  - → Exemptions By AABB for Accredited Labs Internationally
  - → Accepted by AABB as an alternative in the US
- Replacement of CMV testing
- Extension of platelet shelf life to 7 days, when that is allowed
- Satisfies AABB requirement **5.1.5.1,** as an alternative to BD
- Approved PI claims

INTERCEPT Blood Systems for All components

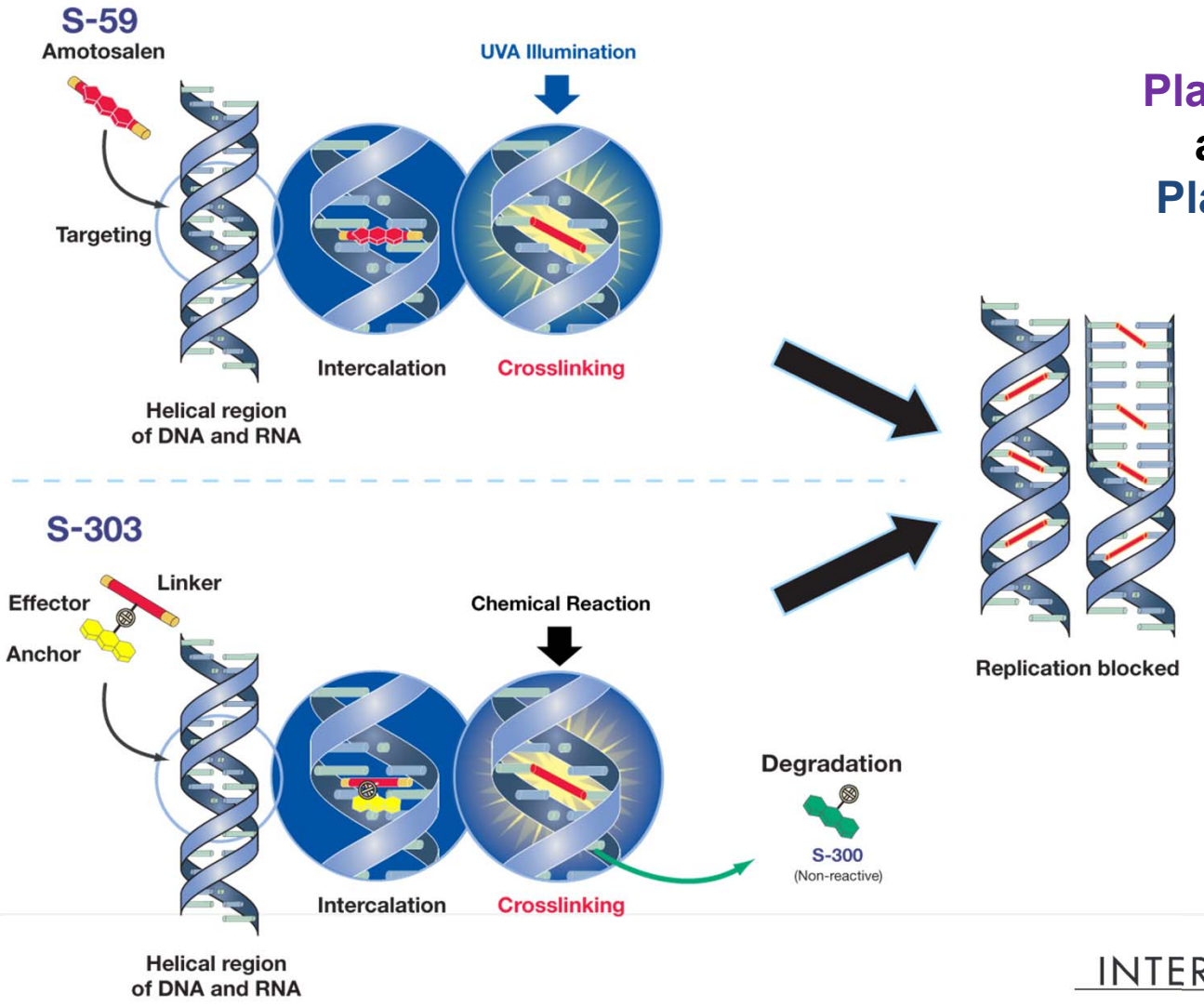
for Platelets

for Plasma

for RBC[1]

[1]The INTERCEPT System for RBC is not approved for use

Common Mechanism of Action and Target Different compounds for PC/PL and RBC



Platelets
and
Plasma

RBC

Agents Inactivated by INTERCEPT (Amotosalen)

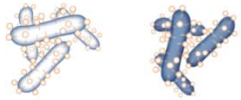
ROUTINELY TESTED AGENTS

ENVELOPED VIRUSES

HIV-1
HIV-2
HBV
HCV
HTVL-I
HTLV-II

SPIROCHETES

Treponema pallidum



BACTERIA

CERUS'S COMPREHENSIVE SPECTRUM PROTECTION

ENVELOPED VIRUSES

HIV-1
HIV-2
HBV
HCV
HTVL-I
HTLV-II

BVDV
CMV
WNV
SARS
Vaccinia[1]
Chikungunya
Dengue[2]
Influenza A

DH BV

NON-ENVELOPED VIRUSES

Bluetongue virus, type 11
Simian Adenovirus-15
Feline calicivirus
Parvovirus B19
Human adenovirus 5

GRAM-NEGATIVE BACTERIA

Klebsiella pneumoniae
Yersinia enterocolitica
Escherichia coli
Pseudomonas aeruginosa
Salmonella choleraesuis
Enterobacter cloacae
Serratia marcescens
Anaplasma phagocytophilum
Orientia tsutsugamushi[3]

GRAM-POSITIVE BACTERIA

Staphylococcus epidermidis
Staphylococcus aureus
Streptococcus pyogenes
Listeria monocytogenes
Corynebacterium minutissimum
Bacillus cereus (vegetative)
Lactobacillus sp.
Bifidobacterium adolescentis
Propionibacterium acnes
Clostridium perfringens

SPIROCHETES

Treponema pallidum
Borrelia burgdorferi

PROTOZOA

Trypanosoma cruzi
Plasmodium falciparum
Leishmania sp.
Babesia microti

LEUKOCYTES

T-cells

(1) Sampson-Johannes A, et al. 2003. *Transfusion*. 43:83A; (2) Lam S, et al. *Transfusion* 2007;47:134A; (3) Rentas F. *Transfusion* 2004;44:104A.

INTERCEPT BLOOD SYSTEM

Agents Inactivated by INTERCEPT (Amustaline)

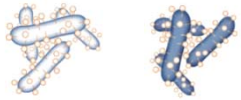
ROUTINELY TESTED AGENTS

ENVELOPED VIRUSES

HIV-1
HIV-2
HBV
HCV
HTVL-I
HTLV-II

SPIROCHETES

Treponema pallidum



BACTERIA

CERUS'S COMPREHENSIVE SPECTRUM PROTECTION

ENVELOPED VIRUSES

HIV-1
HIV-2
HBV
HCV
HTVL-I
HTLV-II

BVDV
CMV
WNV
SARS
Vaccinia[1]
Chikungunya
Dengue[2]
Influenza A

DH BV

NON-ENVELOPED VIRUSES

Bluetongue virus, type 11
Simian adenovirus 15
Feline calicivirus
Parvovirus B19
Human Adenovirus 5

GRAM-NEGATIVE BACTERIA

Klebsiella pneumoniae
Yersinia enterocolitica
Escherichia coli
Pseudomonas aeruginosa
Salmonella choleraesuis
Enterobacter cloacae
Serratia marcescens
Anaplasma phagocytophilum
Orientia tsutsugamushi[3]

GRAM-POSITIVE BACTERIA

Staphylococcus epidermidis
Staphylococcus aureus
Streptococcus pyogenes
Listeria monocytogenes
Corynebacterium minutissimum
Bacillus cereus (vegetative)
Lactobacillus sp.
Bifidobacterium adolescentis
Propionibacterium acnes
Clostridium perfringens

SPIROCHETES

Treponema pallidum
Borrelia burgdorferi

PROTOZOA

Trypanosoma cruzi
Plasmodium falciparum
Leishmania sp.
Babesia microti

LEUKOCYTES

T-cells

(1) Sampson-Johannes A, et al. 2003. *Transfusion*. 43:83A; (2) Lam S, et al. *Transfusion* 2007;47:134A; (3) Rentas F. *Transfusion* 2004;44:104A.

INTERCEPT BLOOD SYSTEM

Hemovigilance Programs

Demonstrated safety in routine use

>300,000 INTERCEPT Platelets Evaluated in Routine Use

	French National Hemovigilance[1]	Swiss National Hemovigilance[2]	Multicenter Cerus HV[3]
# INTERCEPT Platelet Transfusions	**180,762**	**130,843**	**19,175**
# Patients Receiving INTERCEPT Platelets	~30,000	~20,000	4,067
INTERCEPT ATR Rate	~0.3%[4]	~0.3%[5]	~0.6%
Conventional ATR Rate	~0.3%[4]	~0.4%[5]	NA

(1) French National Agency for Medicine and Health Product Safety/ANSM, Hemovigilance Activity Reports, 2006 - 2014. (2) SwissMedic Haemovigilance Annual Reports, 2010 - 2014. (3) Knutson F et al. Vox Sanguinis 2015. (4) French National Agency for Medicine and Health Product Safety/ANSM, Hemovigilance Activity Reports, 2009-2011. (5) SwissMedic Haemovigilance Annual Report 2014; conventional : 2008-2010, INTERCEPT: 2011-2014.

INTERCEPT BLOOD SYSTEM

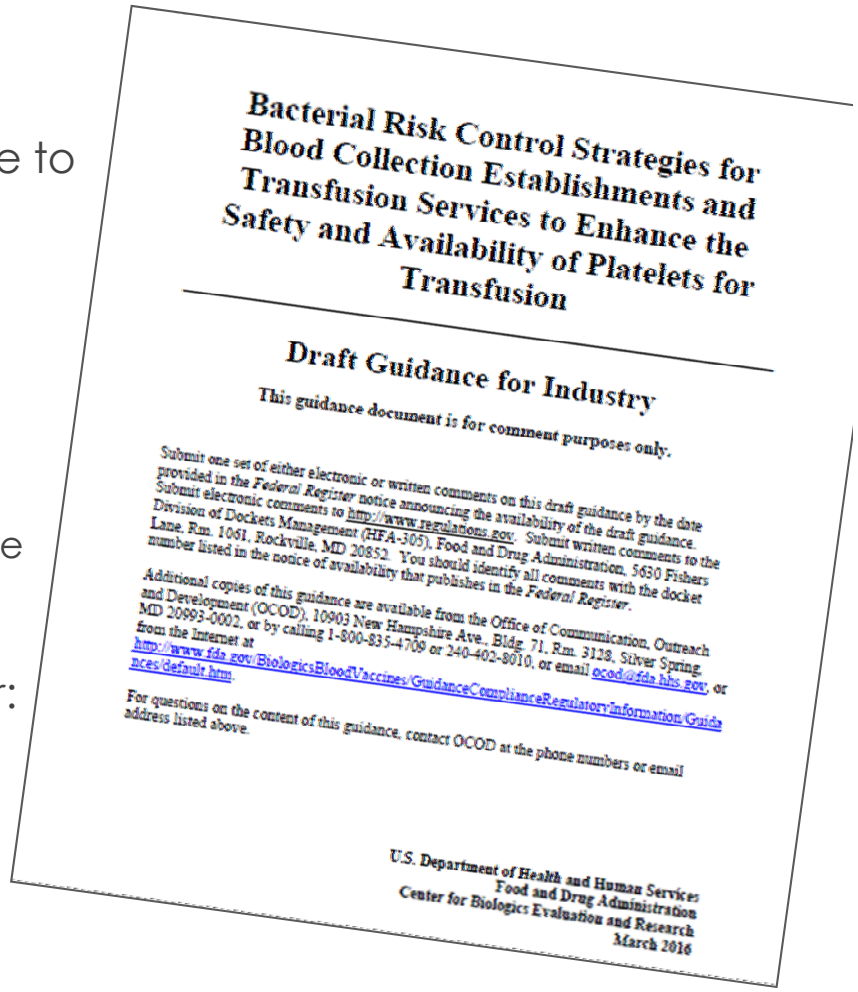
BACTERIA

FDA Revised Draft Guidance for Bacterial Safety[1]

Recognizes bacterial risk in platelets, includes pathogen reduction as option to help mitigate risk

- Addresses industry concerns on the high risk of bacterial contamination in platelets.
- Includes pathogen reduction as an alternative to testing, strengthens language for day 4 and 5 secondary testing requirements.

- Draft Guidance includes:
  - Blood centers - must either:
    - Perform **pathogen reduction**, or
    - Perform primary bacterial testing (use of culture detection method on a sample taken ≥24 hours post-collection)
  - Hospital transfusion service – can use either:
    - **Pathogen reduced** platelets – no further measures necessary
    - Conventional platelets, already negative in primary bacterial testing -- must perform secondary testing at day 4 and 5 per methods in guidance document



Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion

Draft Guidance for Industry

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
March 2016

1. "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion," FDA Draft Guidance for Industry, March 2016.

INTERCEPT BLOOD SYSTEM
PATHOGEN REDUCTION SYSTEM

High Log Inactivation for Broad Spectrum of Bacteria in Platelet Concentrates

Gram-positive (Aerobes and Anaerobes)	PC/PAS	PC/PL	Gram-negative	PC/PAS	PC/PL
Staphylococcus epidermidis	> 6.6	>7.4[1]	Escherichia coli	> 6.4	≥7.3
Staphylococcus aureus	6.6	>7.6	Serratia marcescens	> 6.7	>7.1
Streptococcus pyogenes	> 6.8	>6.1	Klebsiella pneumoniae	> 5.6	≥6.7
Listeria monocytogenes	> 6.3	>6.6	Pseudomonas aeruginosa	4.5	≥6.8
Corynebacterium minutissimum	> 6.3	>6.4	Salmonella choleraesuis	> 6.2	>5.9
Bacillus cereus (vegetative)	> 6.0	≥5.6	Yersinia enterocolitica	> 5.9	>7.3
Lactobacillus sp	> 6.9	>6.1	Enterobacter cloacae	5.9	≥6.0
Bifidobacterium adolescentis	> 6.5	-	**Spirochetes**		
Propionibacterium acnes	> 6.7	>6.7	Treponema pallidum	6.8 - 7.0	-
Clostridium perfringens	> 7.0	>6.0	Borrelia burgdorferi	> 6.8	-

- **Robust Inactivation of Bacteria is critical to protect against them, as bacteria can grow in blood products**
- [1] In blue latest claims that have not been reviewed by TUV yet

Lin et al: Transfusion 2004;44:1496-1504 and Singh et al: Transfusion 2006;46:1168-1177

INTERCEPT BLOOD SYSTEM

No Sepsis Fatalities with INTERCEPT Platelets when Used in Routine

French and Swiss National hemovigilance data

	Conventional Platelets		INTERCEPT Platelets	
Year	Units Transfused (n)	Transfusion Transmitted Infections (Fatalities)	Units Transfused (n)	Transfusion Transmitted Infections (Fatalities)
2006	231,853	4 (0)	6,420	0 (0)
2007	232,708	9 (2)	15,393	0 (0)
2008	239,349	6 (1)	15,544	0 (0)
2009	241,634	9 (0)	21,767	0 (0)
2010	253,149	2 (1)	22,632	0 (0)
2011	267,785	3 (1)	22,392	0 (0)
2012	275,834	7 (2)	24,849	0 (0)
2013	278,234	4 (1)	25,089	0 (0)
2014	278,788	5 (0)	26,676	0 (0)
2010	29,900	1 (0)	0	0 (0)
2011	6,600	0	26,500	0 (0)
2012	0	0	34,265	0 (0)
2013	0	0	34,750	0 (0)
2014	0	0	35,328	0 (0)
Total	**2,335,834**	**50 (8)**	**311,605**	**0 (0)**

French HV data: 2006-2011: Sweeney J, Lozano M. Platelet Transfusion Therapy. Bethesda: AABB Press, 2013.
2012-2014: French National Agency for Medicine and Health Product Safety/ANSM, Hemovigilance Activity Reports.
Swiss HV data: SwissMedic Haemovigilance Annual Reports, 2010-2014.

INTERCEPT BLOOD SYSTEM

EMERGING PATHOGENS

Emerging Pathogens

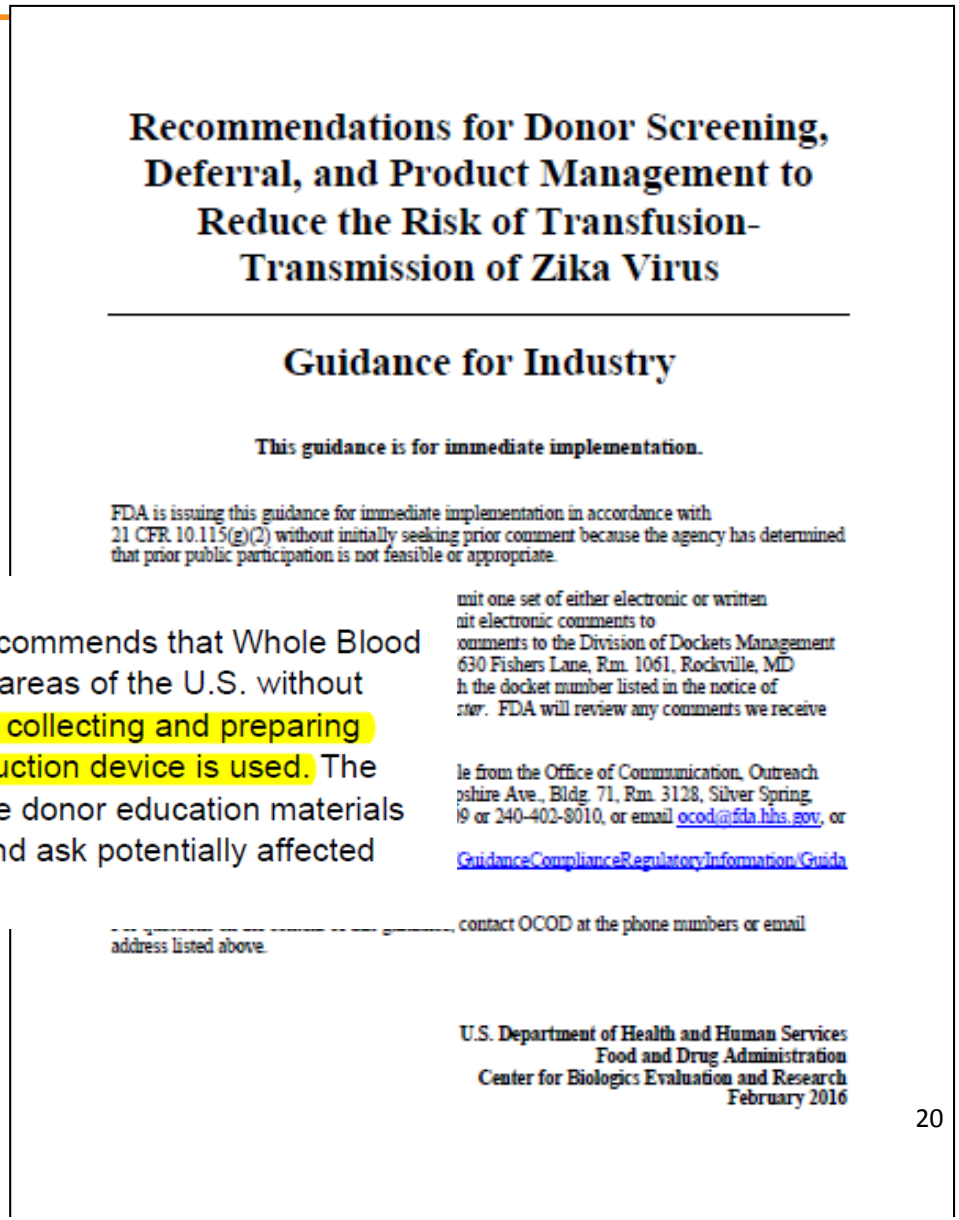
The risk of spreading pathogens – Chikungunya, Dengue, Zika

Emerging Pathogens

Current mitigations: Pathogen Reduction

FDA Guidance, February 2016

*In **areas with active Zika virus transmission (http://www.cdc.gov/zika/geo/index.html)**, the FDA recommends that Whole Blood and blood components for transfusion be obtained from areas of the U.S. without active transmission. Blood establishments may continue collecting and preparing platelets and plasma if an FDA-approved, pathogen-reduction device is used. The guidance also recommends blood establishments update donor education materials with information about Zika virus signs and symptoms and ask potentially affected donors to refrain from giving blood.*



Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion-Transmission of Zika Virus

Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2) without initially seeking prior comment because the agency has determined that prior public participation is not feasible or appropriate.

mit one set of either electronic or written
nit electronic comments to
omments to the Division of Dockets Management
630 Fishers Lane, Rm. 1061, Rockville, MD
h the docket number listed in the notice of
ster. FDA will review any comments we receive

le from the Office of Communication, Outreach
pshire Ave., Bldg. 71, Rm. 3128, Silver Spring,
9 or 240-402-8010, or email ocod@fda.hhs.gov, or

GuidanceComplianceRegulatoryInformation/Guida

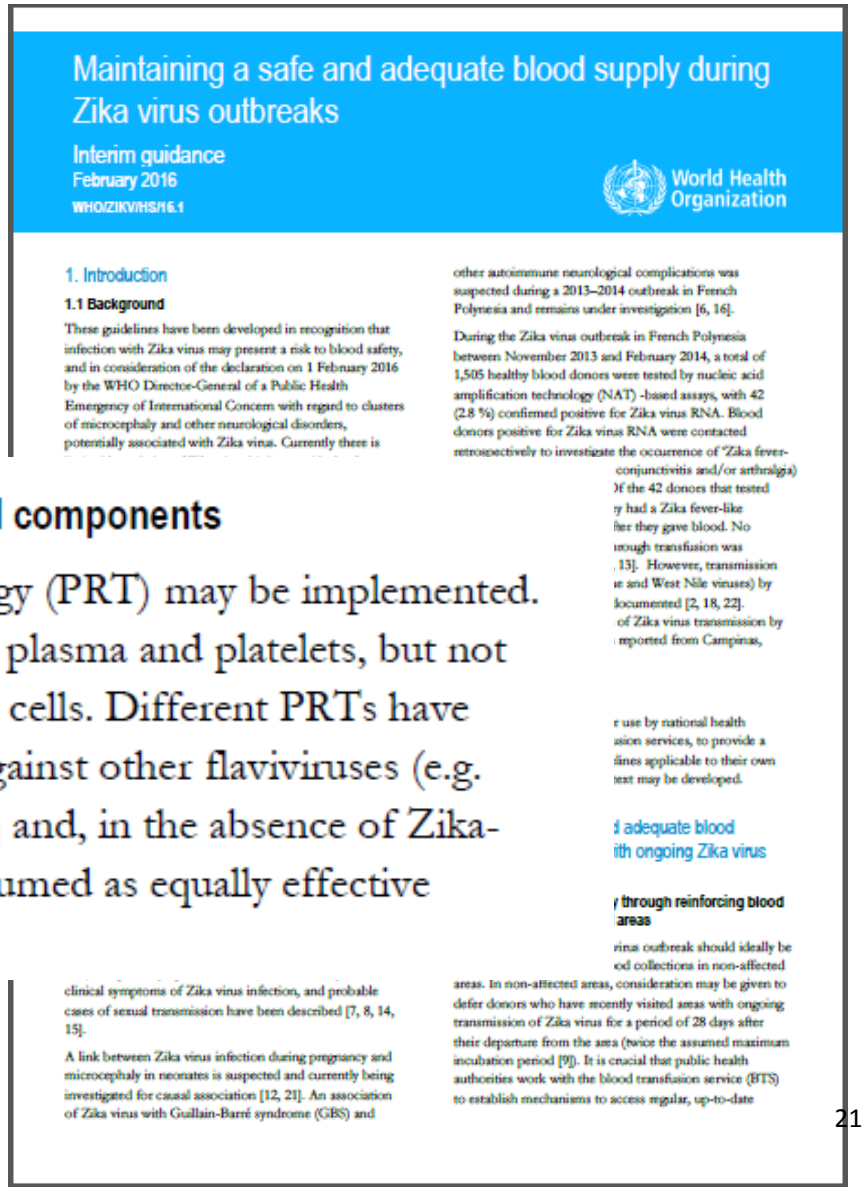
, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
February 2016

Emerging Pathogens

Current mitigations: Pathogen Reduction

WHO Guidance, February 2016



Maintaining a safe and adequate blood supply during Zika virus outbreaks

Interim guidance
February 2016
WHO/ZIKV/HS/16.1

World Health Organization

1. Introduction

1.1 Background

These guidelines have been developed in recognition that infection with Zika virus may present a risk to blood safety, and in consideration of the declaration on 1 February 2016 by the WHO Director-General of a Public Health Emergency of International Concern with regard to clusters of microcephaly and other neurological disorders, potentially associated with Zika virus. Currently there is

other autoimmune neurological complications was suspected during a 2013–2014 outbreak in French Polynesia and remains under investigation [6, 16].

During the Zika virus outbreak in French Polynesia between November 2013 and February 2014, a total of 1,505 healthy blood donors were tested by nucleic acid amplification technology (NAT) -based assays, with 42 (2.8 %) confirmed positive for Zika virus RNA. Blood donors positive for Zika virus RNA were contacted retrospectively to investigate the occurrence of 'Zika fever-

conjunctivitis and/or arthralgia)

Of the 42 donors that tested

y had a Zika fever-like

ter they gave blood. No

rough transfusion was

13]. However, transmission

e and West Nile viruses) by

documented [2, 18, 22].

of Zika virus transmission by

reported from Campinas,

e use by national health

sion services, to provide a

lines applicable to their own

ext may be developed.

l adequate blood

ith ongoing Zika virus

through reinforcing blood

areas

rus outbreak should ideally be

od collections in non-affected

areas. In non-affected areas, consideration may be given to defer donors who have recently visited areas with ongoing transmission of Zika virus for a period of 28 days after their departure from the area (twice the assumed maximum incubation period [9]). It is crucial that public health authorities work with the blood transfusion service (BTS) to establish mechanisms to access regular, up-to-date

clinical symptoms of Zika virus infection, and probable cases of sexual transmission have been described [7, 8, 14, 15].

A link between Zika virus infection during pregnancy and microcephaly in neonates is suspected and currently being investigated for causal association [12, 21]. An association of Zika virus with Guillain-Barré syndrome (GBS) and

c. Pathogen reduction of blood components

Pathogen reduction technology (PRT) may be implemented. PRT is currently available for plasma and platelets, but not for whole blood or red blood cells. Different PRTs have been shown to be effective against other flaviviruses (e.g. West Nile, dengue) [10,11,20] and, in the absence of Zika-specific information, are presumed as equally effective against Zika virus.

The INTERCEPT Blood System

Maintaining a safe and adequate blood supply during arboviral outbreaks

INTERCEPT has been called upon to help sustain platelet availability during arboviral outbreaks:

- 2005 CHIKV epidemic on Ile de La Réunion, France[1]
  - All PC were treated with INTERCEPT allowing collections of PC in the island
- CHIKV outbreaks in Guadeloupe and Martinique, French Polynesia[2]
  - PC were treated with INTERCEPT
  - Other components were either quarantined with enhanced PDI collection, or tested with NAT
  - CHIKV positive donations was transfused to 10 recipients without clinical symptoms[3]
- 2014 CHIKV and DENV outbreaks in the Caribbean region[4]
  - INTERCEPT PC components were deployed in Puerto Rico in response to the epidemic
  - Authorities excluded PI treated components from the quarantine imposed to other components
- 2016 WHO[5] and US FDA[6] issued guidances recommending pathogen reduction as an option to mitigate risks related to ZIKV outbreaks; AABB[7] issued guidance as an option to mitigate CHIKV, DENV, ZIKV

1. Rasongles P, et al. Transfusion 2009;49:1083-91. 2. Musso D, et al.Transfusion. 2014 Nov;54(11):2924-30.3. Gallian et al. Transfusion, sup 3 17A, 2015 4.Rico, S et al. Treatment Use Study of INTERCEPT Platelet Components in Response to the Chikungunya and Dengue Epidemic in Puerto Rico: TRUE Study. presented at BMT Tandem Meeting; February 2016. 5. WHO Interim guidance WHO/ZIKV/HS/16.1 February 2016. 6. FDA Zika Guidance for Industry February 2016. 7. AABB Association Bulletin #16-04. March 1, 2016.

INTERCEPT BLOOD SYSTEM

Arbovirus Comparison

Characteristic	Dengue	Chikungunya	Zika	West Nile
Virus family	Flaviviridae	Togaviridae	Flaviviridae	Flaviviridae
Virus genus	Flavivirus	Alphavirus	Flavivirus	Flavivirus
Serotypes	4	1	1	1
RNA size (kb)	10.7	11.8	10.8	10.3
Vector	*Aedes aegypti* *Aedes albopictus*	*Aedes aegypti* *Aedes albopictus*	*Aedes aegypti* *Aedes albopictus*	*Culex Pipiens* *C. Tarsalis* *C. quinequefasciaatus*
Symptoms / illness	Acute febrile illness	Acute febrile illness	Acute febrile illness	Acute febrile illness, rash
Symptomatic: Asymptomatic	25:75	75:25	**20:80** **Sexually Transmmited**	20:80
Illness outcome	Severe dengue – plasma leakage	Rarely severe, Arthralgias	Rarely severe, Guillian-Barré Microcephaly	Neuroinvasive Disease Meningitis Encephalitis Polyomyelitis

INTERCEPT BLOOD SYSTEM

Pathogen Inactivation of Arboviruses in Plasma by the INTERCEPT Blood System

Arbovirus	Genus	INTERCEPT Log_{10} Reduction
West Nile Virus	Flavivirus	**>6.8**
Dengue	Flavivirus	**>5.6**[1]
Chikungunya	Alphavirus	**>6.4**
Zika	Flavivirus	**>6.6**[2]

[1] Musso D. et al, Transfusion. 2014 54, 2924-30
[2] Aubry M. *et al.* Transfusion, 2016

Published Zika PI in INTERCEPT Plasma

TABLE 1. Detection of replicative ZIKV and ZIKV titration (log $TCID_{50}$/mL) in plasma samples before and after inactivation

Plasma samples	Initial viral titers	Replicative ZIKV after: First passage	Second passage	Third passage	Fourth passage	Fifth passage	Log reduction
A							
Preinactivation sample	6.46	+*	+	+	+	+	>6.46
Inactivated sample	−†	−	−	−	−	−	
B							
Preinactivation sample	6.63	+	+	+	+	+	>6.63
Inactivated sample	−	−	−	−	−	−	
C							
Preinactivation sample	6.61	+	+	+	+	+	>6.61
Inactivated sample	−	−	−	−	−	−	
D (control)							
Preinactivation sample	6.14	+	+	+	+	+	
Noninactivated sample	6.28	+	+	+	+	+	

* Positive immunofluorescence.
† Negative immunofluorescence.

>6.57 Infectivity

TABLE 2. ZIKV RNA quantitation (log copies/mL) in plasma samples before and after inactivation

Plasma sample	Initial RNA loads	RNA loads after: First passage	Second passage	Third passage	Fourth passage	Fifth passage
A						
Preinactivation sample	10.22	10.31	10.08	10.36	10.17	10.48
Inactivated sample	9.67	4.07	ND*	ND	ND	ND
B						
Preinactivation sample	10.41	10.30	10.17	10.26	10.22	10.42
Inactivated sample	9.44	3.63	ND	ND	ND	ND
C						
Preinactivation sample	10.11	10.43	10.19	10.30	10.20	10.65
Inactivated sample	9.41	3.87	ND	ND	ND	ND
D (control)						
Preinactivation sample	10.36	10.26	10.02	10.32	10.02	10.28
Noninactivated sample	9.90	9.89	9.99	9.95	10.18	10.01

* ZIKV RNA not detected.

10.25 PCR

[1]Aubry *et al.* Transfusion 2015

Translating Infectivity to Detection Language[1]

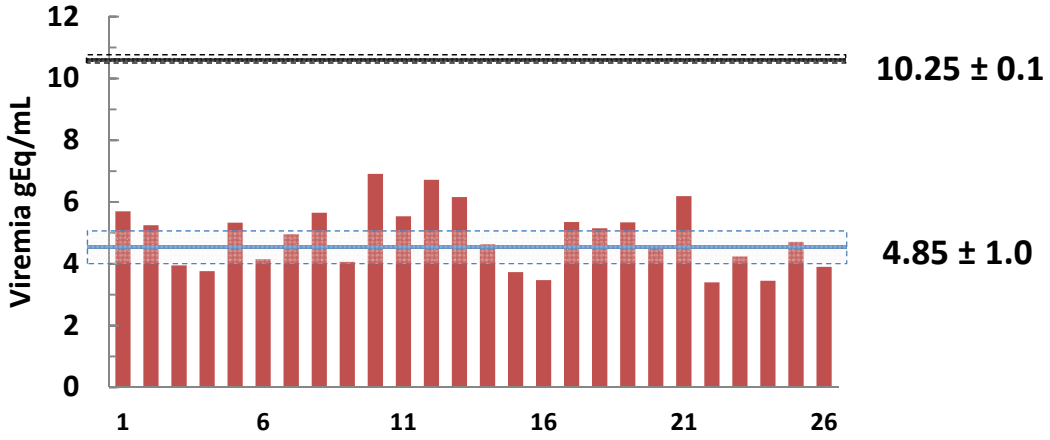
Zika Infectivity PI (cfu/mL) **>6.57 log_{10}**

Zika PCR Reduction (gEq/mL) **10.25 log_{10}**

Log_{10} (gEq/mL)≥3.68 + Log_{10} (CFU/mL)

Inactivation in INTERCEPT Plasma

Donor Viremia



[1]Aubry *et al.* Transfusion 2015

Zika Inactivation using the INTERCEPT System for Platelets

Conditions	N	Log Titers (pfu/mL)		Log Reduction per mL	Log Reduction
		Pre-UVA	Post-UVA		
PC in 100% PLASMA	1	4.3	< 0.0	> 4.3	> 4.3
PC in 65% PAS	2	4.0	<-1.0	>4.0	>4.9
PC in 65% PAS*	2	6.2	<-0.6	>6.2	>6.8

*Small volumes

Zika Inactivation using the INTERCEPT System for Red Blood Cells with S-303

Replicate	Log Titers (pfu/mL)			
	Control	Test	Log Reduction per mL	Log Reduction
1 LR	4.3	<-0.7	>4.3	>5.0
2 LR	4.4	<-0.7	>4.4	>5.1
3 NLR	4.3	<-0.7	>4.3	>5.0
Mean	4.3	<-0.7	>4.3	>5.0

Conducted at nominal volumes (~280 mL AS-5 RBC)

INTERCEPT BLOOD SYSTEM

Conclusions

- Blood Safety is ensured through the use of multiple redundant measures, with testing currently being a key contributor to enhanced blood safety
- There are areas where testing appears inadequate, or cannot be developed and applied fast enough
- PI is increasingly recognized as a technology that can address such areas, as examples from the bacterial contamination and emerging pathogens have demonstrated, in routine use.
- The introduction of PI for RBC will expand the applicability of PI in enhancing blood safety

Thank you!

CERUS