Pathogen Reduction: Coming Sooner Than Expected

Philippine Association of Medical Technologists
Northern California Chapter
Winter CE Seminar – March 5, 2016

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Clinical Professor, UC Davis School of Medicine
Objectives

• Define pathogen reduction
• Summarize history of pathogen reduction utilization plus research performed to date
• Describe pathogen reduction methods currently being investigated or in use
• Predict future impact of pathogen reduction on transfusion medicine practices
Conflicts of Interest

I have no relevant financial relationships with commercial interests that might factor into the content of this presentation.
Pathogen Inactivation: Then, Now, and Soon

Outline

- Definition and rationale
- Historical perspective
- Review of methods that are:
  - Under investigation
  - Being used
- The (potential) future
- Summary
Pathogen Inactivation: Then, Now, and Soon

References

➢ Primary


➢ Secondary

▪ Many – Referred to during course of talk.
Pathogen Inactivation: Then, Now, and Soon

Definition and Rationale
Pathogen Inactivation: Then, Now, and Soon “Spoiler” Slide

Take-Home Messages

• Pathogen inactivation: Used on plasma derivatives for decades
• Application to blood products = much more recent
  o Many potential benefits – e.g., ↑’d safety, predictable dosing, (eventually favorable???) ROI
  o Some disadvantages – e.g., ↓’d efficacy and ↑’d cost (at first)
• Pathogen inactivation of blood products exists in U.S. – i.e.,
  o Octaplas (plasma)
  o INTERCEPT (platelets and plasma)
• More options are on immediate horizon for:
  o Plasma
  o Platelets
• Use for RBCs/whole blood = further in future
Pathogen Inactivation: Then, Now, and Soon

Definition

- **Pathogen** = Disease-causing microorganism
- **Inactivation** = Process of making something inactive
- **Pathogen inactivation** = … (I won’t insult you 😊)
- **Synonymous term** = “Pathogen reduction”
Pathogen Inactivation: Then, Now, and Soon

Rationale

Ideal Outcomes

• 100% destruction of all pathogens in blood product without:
  o Deleterious effects on product efficacy
  o Toxicity
• Reasonable price based on value
• Other benefits – e.g., future elimination of:
  • Infectious disease tests
  • Need for irradiation
  • Etc. (???)
Do any such methods exist?

“Well, I want a toilet made out of solid gold, but it’s just not in the cards, now, is it?”

Austin Powers, 1999
Or is it …?
Pathogen Inactivation: Then, Now, and Soon

Rationale

Potential benefits

• ↓’d risk of transfusion transmissible diseases
  o Admittedly, risk already is very small for *most* known major microorganisms – both:
    ▪ Those for which we test
    ▪ Those for which we do not test
  o But how about:
    ▪ Bacteria in platelets and …
    ▪ Unknown/future infectious threats?
• Elimination of some deferrals, tests, and other “stuff,” e.g.,
  o Bacterial detection testing (applies to platelets)
  o Irradiation (RBCs, platelets)
  o Leukoreduction (RBCs, platelets)
Pathogen Inactivation: Then, Now, and Soon

Rationale

Transfusion-transmitted diseases for which we do not test – e.g.,

- 1st confirmed *Ehrlichia ewingii* transfusion case
- J. Regan et al. *Clin Infect Dis* (online: 03/19/13)

Choose your means of transmission??

*E. Ewingii* morula
(Prof. C. Fox, OSU College Vet Med)

*Amblyomma americanum* (OK State Dept of Health)

versus

Platelet Transfusion
Bacterial Contamination in Platelets

- S. Kleinman estimates (based upon his review of studies published to date) ~ 1:1,500 apheresis platelet units still transmit bacterial infections.
- Works out to ~ 1:250 risk for typical platelet recipient (who receives ~ 6 units over treatment course).
- Pathogen inactivation could eliminate almost all of this risk (some spore-forming bacteria excepted).

Pathogen Inactivation: Then, Now, and Soon

Rationale

Unknown/future threats

- If pathogen inactivation had been available universally in 1999, an estimated 4,480 West Nile virus transmissions would not have occurred.


- What else is coming?
  - Zika
  - Etc.

Transfusion

Image adapted from Crawford County Health Department
Pathogen Inactivation: Then, Now, and Soon

Rationale

Real and/or potential drawbacks

- Loss of product efficacy
- Potential for adverse recipient effects
- Cost
Pathogen Inactivation: Then, Now, and Soon

History
Pathogen Inactivation: Then, Now, and Soon
History: For Human-Derived Plasma Derivatives

Human-derived plasma derivatives

- Main “ingredient” comes primarily from paid donors
- Manufactured via fractionation
- Thousands of donors used in many typical pools

From Marketing Research Bureau
(http://mrb.lynxdesign.com/plasma-industry/history-of-plasma-fractionation/ – Accessed 04/20/13)

Yes, you do save lives.  |  www.bloodsource.org  |  not-for-profit since 1948
Infectious diseases due to plasma derivatives

- Manufacturing from pooled plasma → “pooled risk”
- Cohn technique → some protection, especially for:
  - Albumin
  - Immune globulins
- But even the latter two products have carried risk
  - 1973: *Pseudomonas (Burkholderia) cepacia*-contaminated albumin
  - 1977-78: HCV-contaminated Rh immune globulin
  - 1996: *Enterobacter cloacae*-contaminated albumin
Pathogen Inactivation: Then, Now, and Soon
History: For Human-Derived Plasma Derivatives

Infectious diseases due to plasma derivatives

- And clotting factors were once a very special problem
  - By 1985 – Infections in hemophiliacs due to unheated and dry heat-treated Factor VIII were overwhelming
    - Up to 95% of U.S. hemophiliacs were HCV-infected
    - ~ 50% were HIV-infected (~ 90% rate in severe hemophiliacs)
      - Data from National Heart Lung, and Blood Institute
        (http://www.nhlbi.nih.gov/health/prof/blood/other/hemophilia/backgrou.htm)
  - This led to use of a series of pathogen reduction methods
    - Pasteurization (simple heating of albumin 1st done in 1948)
    - Organic solvents + detergents
    - Nanofiltration
    - (also, reduction in pool sizes … up to 400,000 donors were once used!)
Pathogen Inactivation: Then, Now, and Soon

Infectious diseases due to plasma derivatives

- FDA now requires \( \geq 2 \) methods for pathogen inactivation of pooled plasma products
- There now exists a big market for recombinant clotting factors
Until very recently, pathogen inactivation did not have much impact in U.S. on transfusable products (more discussion on use in other countries to follow)

In fact, an earlier iteration of solvent-detergent-treated plasma was a temporary game-changer ...
Pathogen Inactivation: Then, Now, and Soon

History: For Transfusible Blood Products


- 1986/87: B. Horowitz conceived idea of SD plasma
- Worked with NYBC (+ VITEX) and Octapharma on modified version of method used on plasma derivatives
- 1990-1995: Series of clinical trials took place
- 1998: FDA licensure granted (Name: PLAS+SD™)
Pathogen Inactivation: Then, Now, and Soon
History: For Transfusible Blood Products


- **Marketing challenges**
  - American Red Cross (ARC) was granted distribution rights, plus …
  - Only ARC would supply plasma for manufacture and …
  - Price was set 30% higher than expected
  - Intended market was displeased (led to “Donor Re-tested Plasma”)

- **Nonenveloped virus transmission by SD plasma**
  - Parvovirus B19 shown as transmissible when in high concentrations
  - Led to market recalls and …
  - … Start of parvovirus B19 minipool testing (cut-off at $10^4$ GE/mL)
Pathogen Inactivation: Then, Now, and Soon
History: For Transfusible Blood Products

The VITEX Story  (From B. Horowitz. United States/solvent
detergent plasma. In JP Aubuchon, CV Prowse (ed.). Pathogen
Inactivation: The Penultimate Paradigm Shift. AABB Press 2010)

- The Final Straw
  - 1999: Cedars-Sinai Medical Center observed 6 deaths in 32 liver
    transplant patients – cause: hepatic thromboses
  - Four additional, similar deaths occurred in undisclosed location(s)
  - Ascribed to SD plasma
    - No cause-and-effect relationship proven, but
    - SD plasma shown to have low levels of proteins C and S
  - 2002: FDA issued warning not to use SD plasma for liver
    transplant patients (or for those with severe liver disease)
  - Moot issue: VITEX had stopped making SD plasma in 2001
Pathogen Inactivation: Then, Now, and Soon

Current Methods Being Investigated or Used
Pathogen Inactivation: Then, Now, and Soon

Products in Play

<table>
<thead>
<tr>
<th>Method – Name (Manufacturer)</th>
<th>Plasma</th>
<th>Platelets</th>
<th>RBCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent Detergent – OctaPlas® (Octapharma)</td>
<td>X</td>
<td></td>
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<tr>
<td>Solvent Detergent – VIPS Plasma® &amp; Cryo® (VIPS)</td>
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<td>X</td>
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<tr>
<td>Riboflavin + UV – Mirasol® (Terumo BCT)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>UV-C – Theraflex® (Macopharma)</td>
<td>(X)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>S-303 – INTERCEPT™ (Cerus)</td>
<td>---</td>
<td>---</td>
<td>X</td>
</tr>
</tbody>
</table>

Yellow highlight indicates FDA-approved product.
Pathogen Inactivation: Then, Now, and Soon

Energy & Dosing Schema for Plasma and Platelets


<table>
<thead>
<tr>
<th>Color</th>
<th>Wavelength interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>red</td>
<td>~ 700–635 nm</td>
</tr>
<tr>
<td>orange</td>
<td>~ 635–590 nm</td>
</tr>
<tr>
<td>yellow</td>
<td>~ 590–560 nm</td>
</tr>
<tr>
<td>green</td>
<td>~ 560–490 nm</td>
</tr>
<tr>
<td>blue</td>
<td>~ 490–450 nm</td>
</tr>
<tr>
<td>violet</td>
<td>~ 450–400 nm</td>
</tr>
</tbody>
</table>
Solvent Detergent Treatment

- Disrupts lipid membranes, affecting:
  - Enveloped viruses
  - Most bacteria
  - Leukocytes
- First used on pooled plasma derivatives
- Logical extension was to apply it to plasma
- Retains most coagulant activity
- Cannot be used on **cellular blood products**
Pathogen Inactivation: Then, Now, and Soon

Plasma Applications

Solvent Detergent Treatment

- Requires screening for non-lipid-enveloped viruses
  - Parvovirus B19
  - Hepatitis A virus
  - Hepatitis E virus
- Used in numerous countries (now including U.S.)
- Two transfusible products in production
  - OctaPlas®/OctaPlas LG® (Octapharma) – In USA
  - VIPS Plasma and Cryo – In Europe, only
What Is Octaplas?

• Manufactured by Octapharma (in Europe) from pooled human plasma (from U.S. donors) using …
  • … enhanced solvent-detergent treatment process and …
  • … prion removal step (via ligand gel)
• Jan. 17, 2013: FDA approved

“For patients suffering with clotting disorders, this product provides a viable alternative to single-donor Fresh-Frozen Plasma and provides a reduced risk of certain viral transmissions” (Karen Midthun, Director of FDA’s CBER)

From Octapharma Website
What Is Octaplas?

• > 12 million units transfused
• Each lot comes from a single ABO group
• Standardized coagulation factor levels
• Reduced TRALI risk (due to dilutional effect)
• 200 mL fixed doses
• 2-to-4° C storage for up to 12 hours post-thaw

From Octapharma Website
Clinical Indications for Octaplas

FDA-Approved Indications

• Replacement of multiple coagulation factors in patients with acquired deficiencies
  • Due to liver disease
  • Undergoing cardiac surgery or liver transplant
• Plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP)

Note: It is likely that off label use may occur in other settings where plasma is transfused (especially given that it is used interchangeably with traditional plasma in much of the EU).
Manufacture & Related Issues

Manufacturing, Storage, and QC

• 630-1,520 individual donations are thawed/pooled
  • Units from new donors held until donors return for repeat testing
• Filtration through 1 μm pore size membrane
• Treatment with solvent detergent for 1-1.5 hours at 30°C
  • 1% tri(n-butyl) phosphate (TNBF)
  • 1% octoxynol
• SD reagents removed by oil + solid phase extraction
• Resin column-based removal of prions  [... Continued]
Manufacturing, Storage, and QC (cont.)

- After sterile filtration, product goes into sterile blood bags
- Labeled and stored at ≤ 30°C
- Tested for:
  - Factors I, II, V, VII, VIII, X, XI
  - Proteins C and S
  - α2-antiplasmin (= “plasmin inhibitor;” interferes with clot lysis)
  - ADAMTS13
- Stored before use at ≤ 18°C for up to 24 months
# Manufacture & Related Issues

## Infectious Disease Screening

<table>
<thead>
<tr>
<th>Agent (Test)</th>
<th>Limit in Pool</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1/2 (Anti-HIV-1/2)</td>
<td>Negative</td>
</tr>
<tr>
<td>HIV-1/2 (HIV-PCR)</td>
<td>Negative</td>
</tr>
<tr>
<td>HAV (Anti-HAV)</td>
<td>≥ 1 IU/mL</td>
</tr>
<tr>
<td>HAV (HAV-PCR)</td>
<td>Negative</td>
</tr>
<tr>
<td>HBV (HBsAg)</td>
<td>Negative</td>
</tr>
<tr>
<td>HBV (HBV-PCR)</td>
<td>Negative</td>
</tr>
<tr>
<td>HCV (HCV-PCR)</td>
<td>Negative</td>
</tr>
<tr>
<td>HEV (HEV-PCR)</td>
<td>Negative</td>
</tr>
<tr>
<td>Parvovirus B19 (PCR)</td>
<td>≤ 10.0 IU/μL</td>
</tr>
</tbody>
</table>

From Octaplas package insert
## Manufacture & Related Issues

### Effectiveness of Viral Reduction

<table>
<thead>
<tr>
<th>Reduction Step</th>
<th>HIV-1</th>
<th>Pseudorabies Virus (HBV model)</th>
<th>Sindbis Virus (HCV model)</th>
<th>Bovine Viral Diarrhea Virus (HCV model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S/D treatment</td>
<td>≥ 6.18</td>
<td>≥ 5.03</td>
<td>≥ 5.31</td>
<td>≥ 5.12</td>
</tr>
<tr>
<td>Global process</td>
<td>≥ 6.18</td>
<td>≥ 5.03</td>
<td>≥ 5.31</td>
<td>≥ 5.12</td>
</tr>
</tbody>
</table>

From Octaplas package insert
Supporting Studies

Octaplas versus Traditional FFP

- Studies suggest equivalence for labeled indications
- Limitations
  - All have focused almost exclusively on surrogate indicators of clinical efficacy – e.g., pre- and post-transfusion coagulation factor levels (EXCEPTION: a small TTP study)
  - None has compared clinical outcomes or adverse effects in a truly meaningful way
  - Unlikely that any suitably powered randomized controlled studies will be done
Supporting Studies


**Octaplas versus Traditional FFP**

- 28 coagulopathic pre-liver transplant patients randomized to receive FFP or SDT-plasma
- End points: side effects, correction of coagulopathy, and seroconversion for viral markers.
- Equivalency observed for all endpoints
- Use of other blood components (RBCs, platelets) was statistically identical in both groups.
Octaplas versus Traditional FFP

- Compared impact of SDP versus FFP on hemostasis and fibrinolysis in coagulopathy following open-heart surgery
- Patients received either 600 ml of SDP (n = 36) or 600 ml of FFP (n = 31) at an infusion rate of 30 ml/min.
- Multiple coagulation factors assessed pre-transfusion and 60 minutes post-transfusion
- No significant differences in lab hemostasis indicators

Supporting Studies

Supporting Studies

A Heger, et al. Normal levels of ADAMTS13 and factor H are present in the pharmaceutically licensed plasma for transfusion (Octaplas®) and in the universally applicable plasma (Uniplus) in development. Vox Sanguinis 2007; 92: 206-212.

Does Octaplas have normal ADAMTS13 and factor H levels/activities?

- Yes
- From these in vitro results, authors inferred (and implied) that Octaplas may be used for treatment of TTP and aHUS
Supporting Studies


**Octaplas for Treatment of TTP**

- Retrospectively analyzed acute TTP episodes in 8 patients (all positive for anti-ADAMTS13; 7 with severe ADAMTS13 deficiencies) treated with plasma exchange using SDP
- All responded rapidly to SDP plasma exchange with:
  - Increase in platelet count to > 150 × 10^3/uL and
  - Resolution of hemolytic anemia
- Well tolerated with no adverse reactions
Supporting Studies


Prion Elimination and Octaplas

• Assessed new chromatographic step for selectively binding pathological prion proteins (PrP<sup>Sc</sup>) to an affinity ligand
• Led to substantial reduction in PrP<sup>Sc</sup>
• No evidence of loss of in vitro coagulation factor activity

Images from picsearch (left) and tumblr.com (right)
Supporting Studies


Prion Elimination and Octaplas

Bonus: A parallel study – applying reduced S/D treatment times – led to increased plasmin inhibitor levels without sacrificing pathogen inactivation performance
Supporting Studies


**TRALI Risk Reduction**

- For 2-year period, TRALI rates were assessed for transfusion of all blood products
- 85 TRALI cases were utilized in the denominator
  - 62 confirmed
  - 23 possible
- Rate was approximately 1 in 31,000 for traditional plasma
- No TRALI reactions observed for > 200,000 Octaplas units transfused
Benefits & Limitations Of Octaplas

On the Plus Side …

• Further reduction (and probable elimination) of transfusion transmission risk for most microorganisms
  o Good against bugs for which we already test
  o Good against most bugs for which we do not test
  o Good against most emerging/unknown bugs
  o May reduce future need for donor infectious disease tests
  o Probable reduced risk for infectious prions
• Reduced TRALI risk
• Possibly reduced allergic reaction risk
Benefits & Limitations Of Octaplas

On the (In Some Cases Possible) “Flip Side” …

• Limitations to post-thaw condition, e.g.,
  • Storage temperatures (2-to-4°C) and
  • Maximum duration (12 hours)
• Risk for transmission of emerging (especially unrecognized) non-enveloped viruses and/or …
• Risk for transmission of other microorganisms not inactivated effectively by solvent-detergent treatment
Pathogen Inactivation: Then, Now, and Soon

**Plasma Applications**

**Solvent Detergent Treatment**

- **VIPS Medical Products**
  - VIPS Plasma and Cryopoor Plasma
    - 400 mL treatment capacity
  - VIPS Cryo
    - 30-32 units (400 mL) “dry cryoprecipitate”
  - CE marked for single donor and minipools
  - Not available in U.S.

From VIPS Medical Website

(http://vipsmedical.virtua.ch/flyer/VIPS_flyer_plasma_an.pdf) – Accessed 04/20/13
Pathogen Inactivation: Then, Now, and Soon

Plasma Applications

Solvent Detergent Treatment

VIPS Medical Products

From VIPS Medical Website
(http://vipsmedical.virtua.ch/flyer/VIPS_flyer_plasma_an.pdf) – Accessed 04/20/13

Solvent Detergent process (1% TnBP, 1% Triton X-45) at 31°C. Specially designed for mini-pool virus inactivation of plasma for clinical transfusion.

Reagents are removed by natural oil extraction.
Pathogen Inactivation: Then, Now, and Soon

Plasma Applications

Cont.

Solvent Detergent Treatment
VIPS Medical Products

Sterile filtration: remove bacteria, pyrogen, parasites, leucocytes, cell debris and plasma micro-particles.

90% of plasma coagulation factors, coagulation inhibitors as well as albumin and immunoglobulin are recovered with VIPS Plasma.

From VIPS Medical Website
(http://vipsmedical.virtua.ch/flyer/VIPS_flyer_plasma_an.pdf) – Accessed 04/20/13
Pathogen Inactivation: Then, Now, and Soon

Plasma Applications

Methylene Blue + Visible Light

- Theraflex® (Macopharma) CE marked since 2000
- Photodynamic reaction (generation of reactive oxygen species)
- > 1.9 million units transfused in 18 countries
- Single-unit treatment (not available in U.S.)
- Allows for further manufacture of cryoprecipitate
- Generally believed to be safe, though French Hemovigilance system has recognized possible heightened risk of severe allergic reactions
  - France issued safety alert, and …
  - … Switched to use of Intercept® Plasma
Pathogen Inactivation: Then, Now, and Soon

Plasma Applications

Methylene Blue + Visible Light

- Coagulation assays prolonged, with lower [fibrinogen]
- Thrombin generating capacity ↓'d and clotting time ↑'d (though clot strength not affected)
- ??? Whether amount of transfused plasma must be ↑'d

- Treatment of TTP – Reportedly:
  - Requires 2x number of exchanges
  - Associated with 2x recurrent rate

Pathogen Inactivation: Then, Now, and Soon

Plasma Applications

Amotosalen + UV-A

- INTERCEPT® Plasma (Cerus)
- Uses synthetic psoralen – via oxygen-independent photochemical reaction – to crosslink nucleic acids
- CE marked since 2006
- FDA-approved in December 2014
- Single-unit treatment
Pathogen Inactivation: Then, Now, and Soon

Plasma Applications

Riboflavin + Broad Spectrum UV

- Mirasol® (Terumo BCT)
- Photodynamic reaction (via generation of reactive oxygen species) using riboflavin (vitamin B2) substrate
- CE marked since 2008
- Not available in U.S.
- Single-unit treatment
- 20-30% ↓ in procoagulant activity
- Clinical trials limited

Yes, you do save lives. | www.bloodsource.org | not-for-profit since 1948
Pathogen Inactivation: Then, Now, and Soon

Plasma Applications

Final Issues

- For most part there have been mildly reduced coagulation factor levels in all products described
  - Most factors: ≤ 10-15% diminution
  - Some factors (e.g., Factor VIII and fibrinogen): up to 25-35% ↓
  

- Recent comparison of methylene blue, solvent detergent, and quarantine plasma for liver transplant
  - ↑’d rates of hepatic artery thromboses for solvent-detergent plasma
  - ↑’d plasma use for methylene blue

Pathogen Inactivation: Then, Now, and Soon

Platelet Applications

- **Amotosalen + UV-A**
  INTERCEPT™
- **Riboflavin + Broad Spectrum UV**
  Mirasol®
- **UV-C Light**
  Theraflex®
Pathogen Inactivation: Then, Now, and Soon

Platelet Applications

Amotosalen + UV-A

- INTERCEPT™ (Cerus)
- CE marked in 2002/FDA-approved in December 2014
- 600,000 units transfused as of 2012
- EUROSPRITE Study (1° endpoint: 1-hr CCI and CI)
  - No statistical difference in CCIs for experimental vs. control
- SPRINT Trial (1° endpoint: ≥ Grade 2 bleeding)
  - Noninferiority confirmed for 1° endpoint, though …
  - … unfavorable differences found in:
    - 1-hour CCI – 11,100 (experimental) vs. 16,000 (control)
    - Transfusion interval (1.9 vs. 2.4 days)
    - Number of platelet transfusions (8.4 vs. 6.2)
Amotosalen + UV-A (INTERCEPT™)

- Findings of French Hemovigilance system (2006-2011)
  - INTERCEPT™: 0 sepsis cases/10^6 transfusions (n ≈ 104,000)
  - Conventional: 22.5 sepsis cases/10^6 transfusions (n ≈ 1.5 million)

- In some European countries they no longer perform following when using treated platelet products:
  - CMV serologic testing
  - Irradiation
  - Bacterial screening
Riboflavin + Broad Spectrum UV

- Mirasol® (Terumo BCT)
- CE marked in 2007
- 10,000 units transfused as of 2012
- MIRACLE Study (1° endpoint: 1-hr CCI)
  - CCI 24% less than seen in control
  - No statistical differences in bleeding or transfusion requirements
- Canada and other countries just began PREPARES Study (1° endpoint: ≥ Grade 2 bleeding)
UV-C Light

- Theraflex® (Macopharma)
- Narrow bandwidth light leading to formation of pyrimidine dimers
- Registered as class II medical device by EU
- 2015 – Targeted launch date for distribution in Europe (more clinical trials ongoing in meantime)
- Interest exists in using this method in U.S.
Pathogen Inactivation: Then, Now, and Soon

RBC and Whole Blood Applications

- **S-303**
  INTERCEPT™ (Cerus)
- **Riboflavin + UV**
  Mirasol®
Pathogen Inactivation: Then, Now, and Soon

RBC Applications

S-303 (INTERCEPT™)

- Chemical-only treatment
- Frangible Anchor-Linker-Effector (FRALE) compound
- Reacts rapidly with nucleic acid and then degrades
- Recently restarted phase III patient trials (following reformulation required to reduce immunogenicity)
- Acceptable preclinical toxicology and pathogen inactivation rates observed thus far, and …
- Red cell recoveries look encouraging
Riboflavin + UV (Mirasol®)

- UV dose adjusted to penetrate pigmented RBCs/whole blood, i.e.,
  - 6 J/mL_{plasma} (for platelets and plasma) versus
  - 80 J/mL_{RBC} (for whole blood)

- Recovery and survival studies reveal significant loss of viability
- May lead to shortened shelf life
  - 35 days?
  - 28 days?
  - Less?
Pathogen Reduction: Then, Now, and Soon

The Future???
Pathogen Reduction: Then, Now, and Soon

The Future

The momentum is growing

- January 17, 2013: FDA approved OctaPlas® to treat patients with blood clotting disorders
- December, 2014: FDA approved INTERCEPT – 1st for plasma, and …
- Then for platelets
Revisiting Cost Effectiveness

- Conventional cost effectiveness assessments are difficult to carry out
  - Preponderance of hypotheticals
  - Transfusion medicine safety decisions are not often based upon usual analyses (e.g., as for quality-adjusted life years)
- Concern exists over current status of health care – Will this concern (and the realities) lead to our:
  - “Stopping the presses?” Or …
  - Hitting the “slow-down switch?”
Pathogen Reduction: Then, Now, and Soon

Summary
### Pathogen Inactivation: Then, Now, and Soon

**Products in Play**

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<td>X</td>
</tr>
<tr>
<td>UV-C – Theraflex® (Macopharma)</td>
<td>(X)</td>
<td>X</td>
<td>---</td>
</tr>
<tr>
<td>S-303 – INTERCEPT™ (Cerus)</td>
<td>---</td>
<td>---</td>
<td>X</td>
</tr>
</tbody>
</table>

Yellow highlight indicates FDA-approved product.

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Pathogen Inactivation: Then, Now, and Soon
Take-Home Messages

- Pathogen inactivation: Used on plasma derivatives for decades
- Application to blood products = much more recent
  - Many potential benefits – e.g., ↑’d safety, predictable dosing, (eventually favorable???) ROI
  - Some disadvantages – e.g., ↓’d efficacy and ↑’d cost (at first)
- Pathogen inactivation of blood products exists in U.S. -- i.e.,
  - Octaplas
  - INTERCEPT
- More options are on immediate horizon for:
  - Plasma
  - Platelets
- Use for RBCs/whole blood = further in future
Pathogen Reduction: Then, Now, and Soon

Outline

- Definition and rationale
- Historical perspective
- Review of methods that are:
  - Under investigation
  - Being used
- The (potential) future
- Summary
With gratitude to, and respect for, all of my friends and colleagues at PAMET
Thank You ...

Q & A + Other Discussion

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