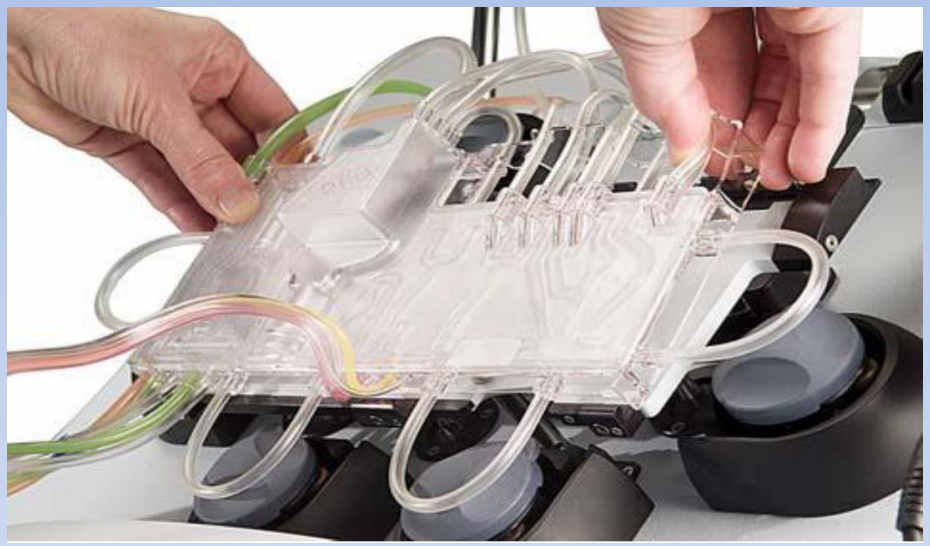
Validation and Qualification of New Equipment for Clinical Applications



Amicus and Optia, the New Generation

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Disclosures

None

Off Label Uses

Filgrastim used under IND for unrelated, allogeneic donations under NMDP protocol

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- Today's Apheresis Devices
- Validation Experience
- Collection Characteristics As Precursors To Biotech Products
- Product Effect On Manufacturing Plans

Fenwal Amicus

Terumo Optia

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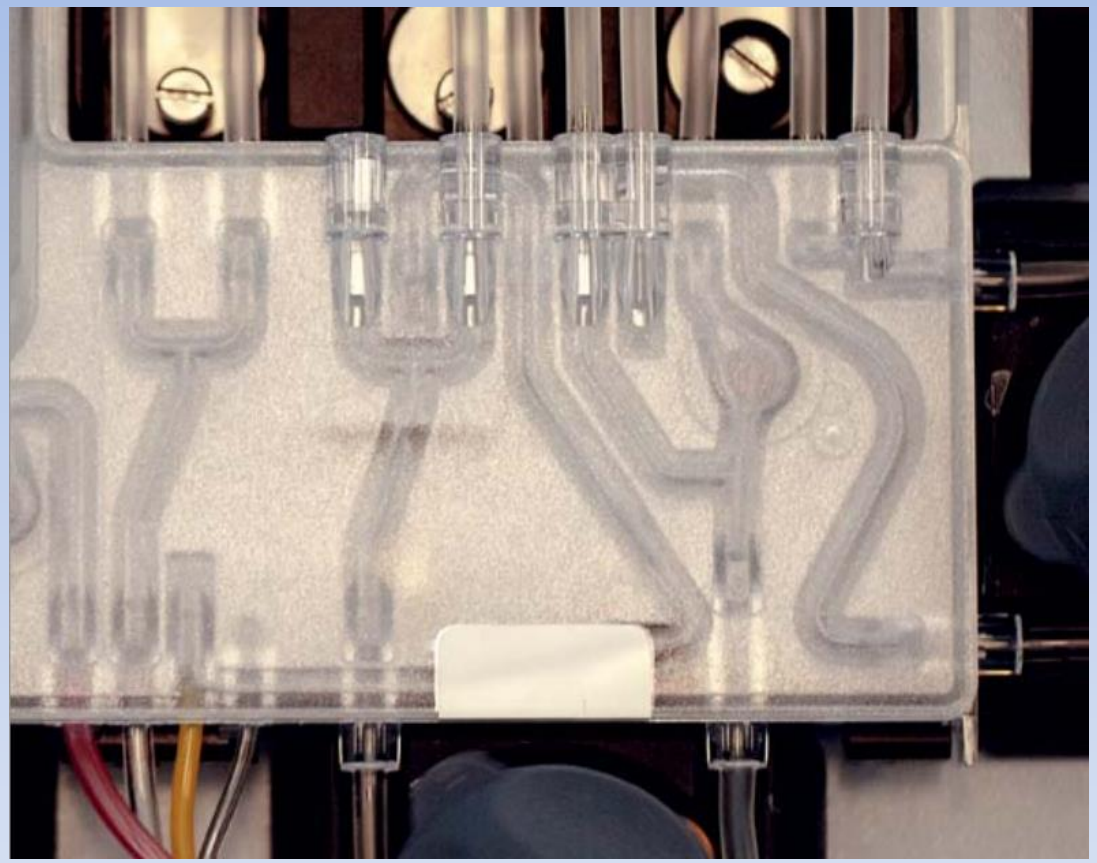
Today's APHERESIS Devices

Evolution of Design



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Uses of Current Apheresis Machines - Collections

Hematopoietic Progenitor Cells, Apheresis (HPC, Apheresis)

- for transplantation cell source
- for $CD34^{+}$ selection and/or expansion
- Granulocyte collection

Mononuclear Cells (MNC)

- for treatment post transplant
- as starting material for other products
- for dendritic cell vaccines

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Apheresis Machines as Collection/Treatment Devices and Laboratory Equipment

COBE Spectra and Fenwal CS3000 were workhorses for plasma exchange, plasma collection, red cell exchange

Both had protocols for selective blood product collection

Both could be used to selectively concentrate or refine other collected products

- Ex. Red cell removal from bone marrow collections in ABO mismatched transplants

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General Rules of Design

The simpler the device:

- More adaptable the device was
- Products were more variable
- Had fewer patient-protecting controls
- Required operator skill
  - Took longer to train staff

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Rules of Technologic Evolution

Devices became more sophisticated

- Computer programs were designed to run specific protocols
- Defined protocols yield consistent products

Improvements were incremental with increasing software control and fewer operator interactions

Basic devices remained relatively stable

Newer Devices Are Highly Engineered

Programming controls the run so that less operator intervention is needed

Higher precision in specific programs decrease adaptability

Patient protections are programmed in:

- Air detectors to prevent air embolism
- Limits on ACD infusion to the patient according to calculated blood volume to prevent Ca^{++} chelation problems

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Engineering Improvement

Spectra Optia is smaller, lighter than COBE Spectra

Kits and software packages are specific to purposes described

Amicus is smaller and lighter than CS 3000

Amicus and Spectra were developed for therapeutic plasma exchange, plasma collection

- Specialized cellular collection programs were added later

What Happens After the Retirement?

Will a single machine replace all the functions of the older machines?

What are the regulatory approvals on the newer devices?

What does each laboratory and treatment center need to do to qualify the new devices?

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Novel Uses Are Going to Different or Older Devices

There is no approved software control package in the Optia or Amicus for buffy coat refinement of bone marrow at this time

The COBE 2991 is still in service in many places

Newer devices, such as the Sepax 2 (Biosafe, Eysins, SW), can be used in labs where they are already in place – usually Cord Blood Banks

Validation Experience

Spectra Optia and Amicus Put to the Test

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Bloodworks NW Validation Plan

A carefully controlled “in process validation” was the practical format

Lab monitoring of each step informed progress of each collection

Data collected allowed us to formulate effective collection processes going forward

Spectra Optia was validated

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Validation Plan

Study the method of operation of the machine

- Electronic data readouts, operational details

Decide on the "**must-haves**" in the new machine

- Safety for the donor (check alarms)
- Sterility of product
- Viability of product
- Yield of apheresis run

Measure what operating parameters will change

- Anticoagulant strategy
- Time of run
- Product volume

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Validation Run Plans

The Performance Qualification can practically be done on patients or allogeneic donors with oversight and controls

Other centers have set up plans – new device is used on patients or donors where multiple collections are planned

- The new and test devices alternate days
- Run unstimulated research donors first to verify approximate collection efficiencies, then $CD34^+$ stimulated subjects

Number of procedures planned: 10 to 50

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Our Approach to Validation

A Sample from the collection bag was taken 2 hours into collection

CD34+ count was done; lab calculated the number of mL of product needed to fulfill the collection goal

- Assumption: the CD34+ content would be stable throughout collection
- Collection time and liters of blood processed were determined by this calculation

ACD only anticoagulant was used as per Optia instructions – no heparin, no aspirin

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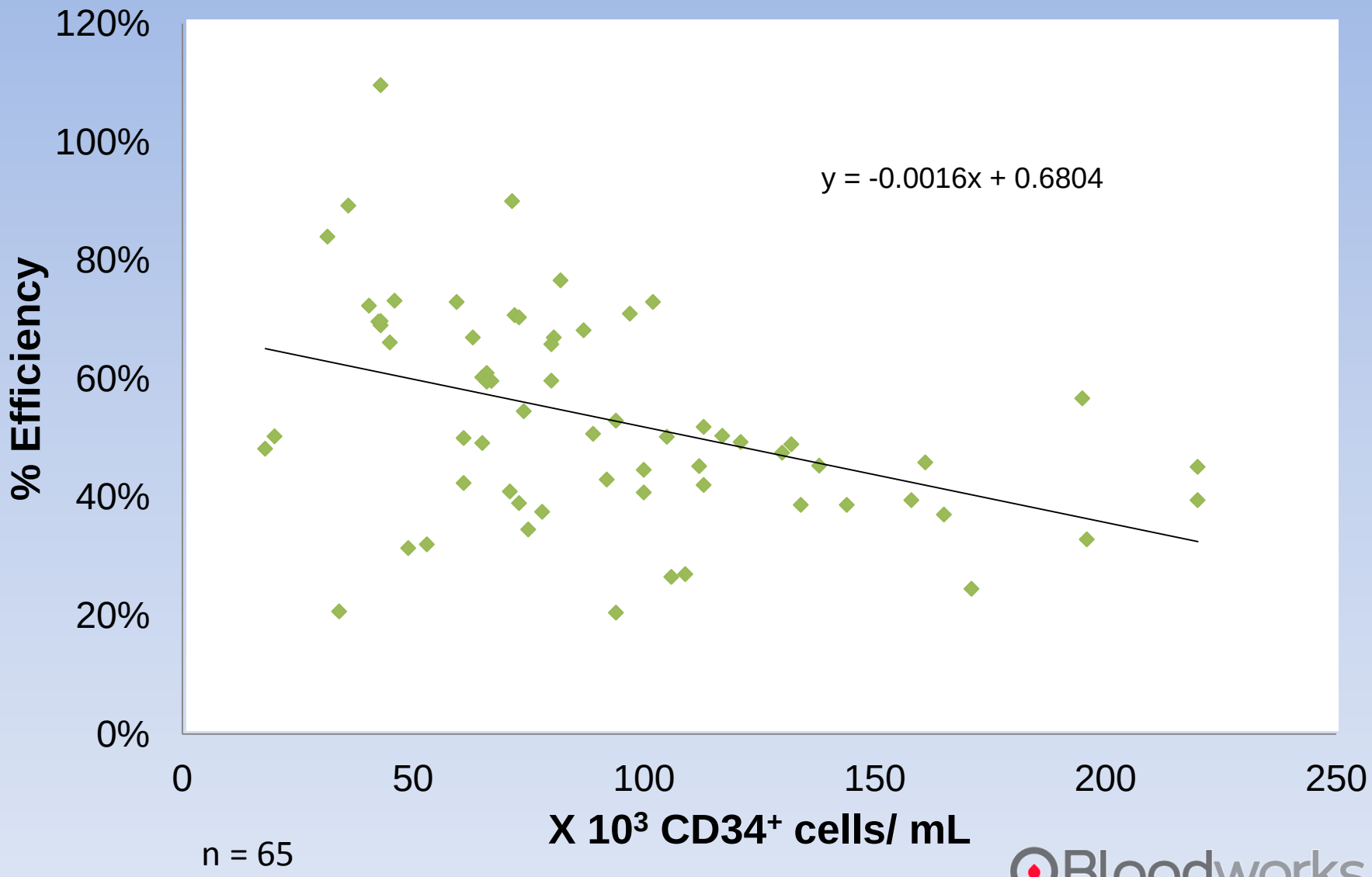
Pre C34+ vs Collection Efficiency



n = 65

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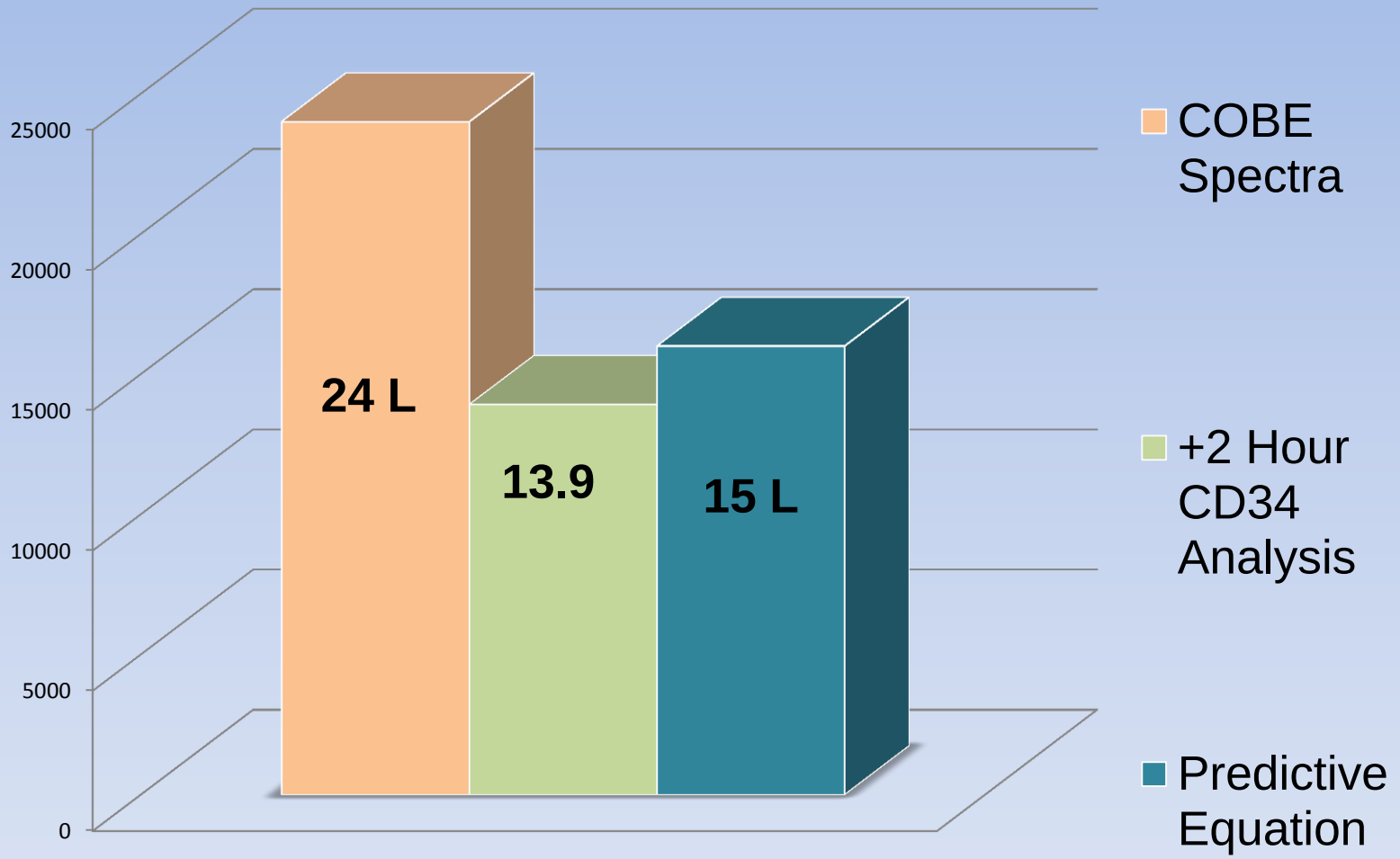
Predictive Equation

Peripheral Blood $CD34^+$ Result	Predictive Equation
< $90x10^3$ cells/ml	$\frac{Goal \times 1.1}{.40} = Target$
≥ $90x10^3$ cells/ml	$\frac{Goal \times 1.1}{.30} = Target$

$$\frac{Target}{Pre\ Result} \times 1000 = Target\ Vol, ml$$

Average Collection Run Volumes



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Optia Validation – Lessons Learned

Predictive CD34+ counts were very valuable

Very high white-count donors, such as NMDP donors, give slightly lower collection efficiencies

Investigators and transplant centers need to order “expected plasma volume” or “minimum plasma volume” instead of “add 200 mL plasma to product”

Orders that are based on volume (xx liters) run through the device are not predictive, need predictive formula

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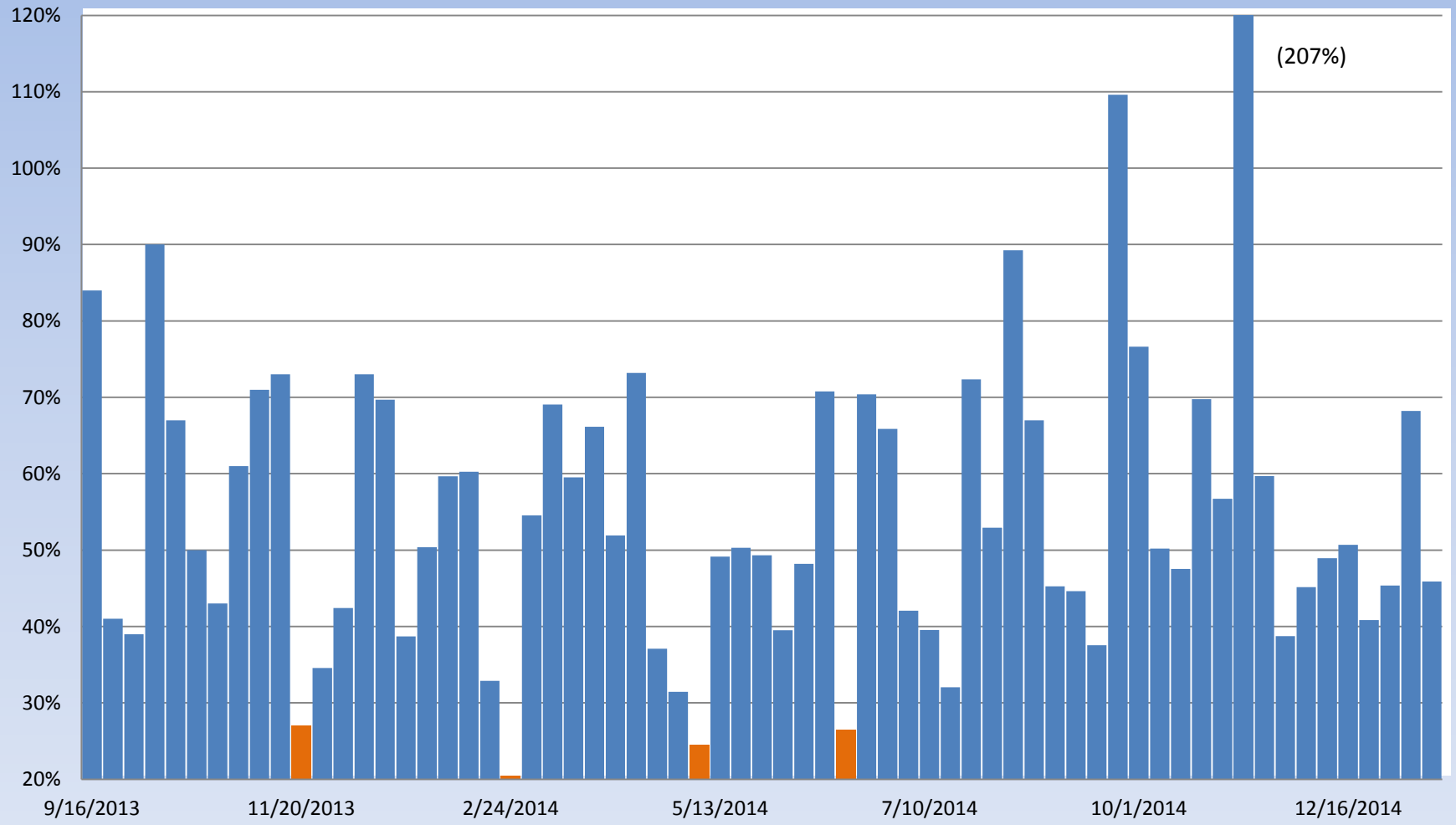
Operator Efficiencies



Amicus Product RBC and Platelet Content

ABO type mismatched allogeneic transplants request <20 mL ABO mismatched red blood cells (RBC)

Company instructions say to expect 15%

Experience of most centers using the device (my survey) reported average hematocrits of 8 to 12%

In a 200+ mL product this is approaching the 20 mL point of caution

Amicus is the most platelet-sparing of the devices

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Amicus Validation – Lessons Learned

Volume of blood processed/min apparently affects collection efficiency

Combination of ACD-A and heparin can be used, but higher flow rates are problematic

Platelets are spared

Hematocrits are higher than Optia products

- One large institution, not measuring directly, estimated at 7 to 9%
- Company information – expect 15%

Bergstaler E et al. J. Clin Apheresis 2011:26;186

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Data Display Characteristics

At the end of the procedure FACT Standards require labeling of the bag with contents before takedown and disconnection from the donor

Amicus does not provide the readout of mL in product or final volume ACD-A

- Product must be removed and weighed
- ACD-A must be calculated

Optia provides data display with the above information on the Graphical User Interface

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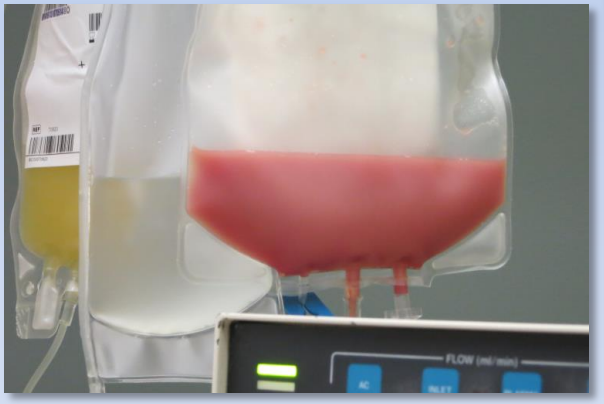
Collection characteristics as precursors to biotech products

Spectra Optia and Amicus: Collection Characteristics



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Requirements for Late Stage Clinical Trial or Licensed Products Raw Material

Qualification of personnel

Qualification process is described by contract

- Continuous exchange of quality metrics between supplier and manufacturer
- Quality Review of your collection operation
  - Site qualification
  - Regulatory status review of your facility
  - Technical assessment of IT system for speed and privacy
- Physical appearance of facility and patient comfort features

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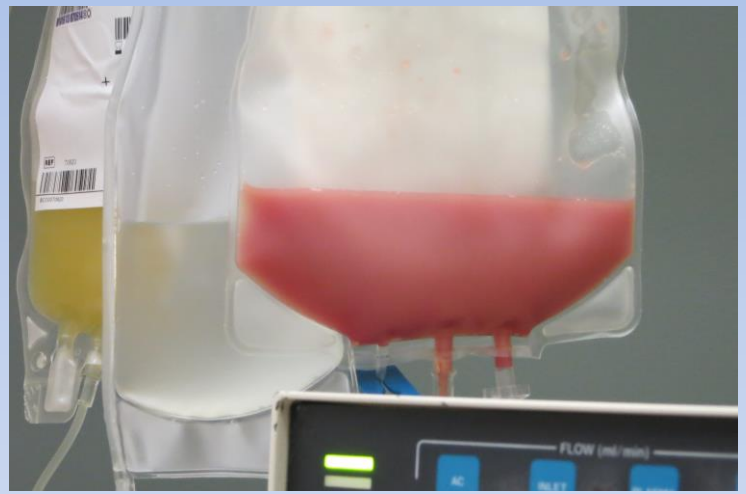
Product and Collection Process Requirements

Example – MNCs for Dendritic Cell Manufacture

- Identification of Donor/Patient
- Method of collection
  - Regulatory qualification of collection device
  - Certification of clinical grade anticoagulants and IV solutions



- # of expected MNC in product
- Product labeled with excipient contents, ex. mL ACD

***Hematocrit < 4%

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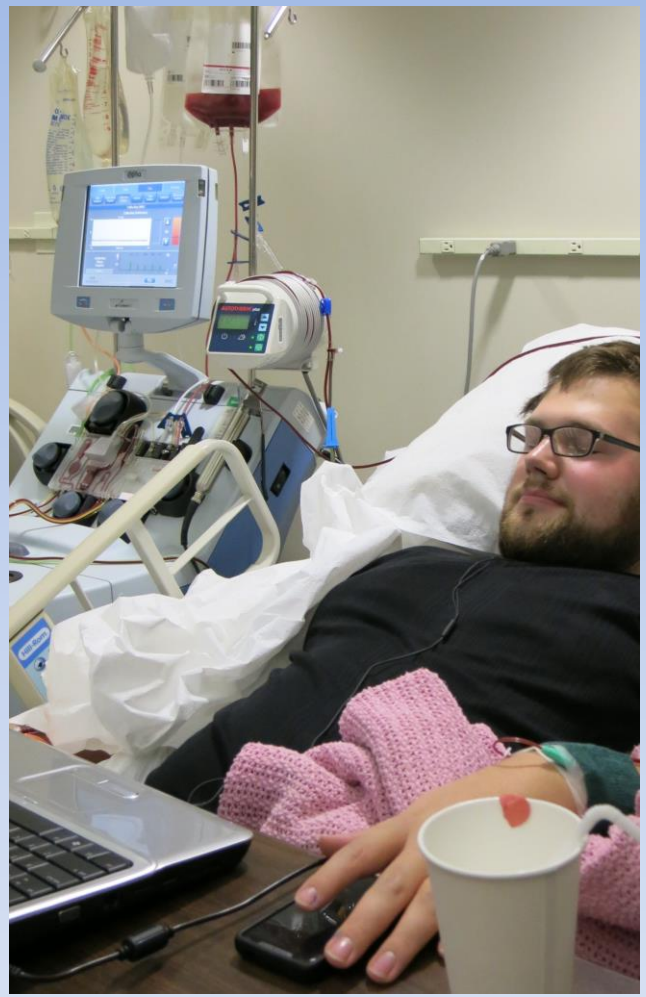
Donor Experience

Differences for the Donor

- Optia - lower volume
- Little citrate toxicity
- Sparing of platelets
- Less time on the machine



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Retrospective: Predicting 40% efficiency

Requested CD34+	Volume Processed	Total CD34+	% of Goal Collected	Efficiency
435	11741	889	204	50.14
144	10573	175	122	43.56
325	14539	478	147	53.03
440	23625	400	91*	65.12
305	8612	801	262	68.90
385	14241	645	168	60.39
732	20030	822	112	50.66

*poor mobilizer

40% efficiency was too conservative

Summary

Newer apheresis devices advantages:

- Smaller size
- Easier portability
- More run automation specific to the procedure selected
- Higher efficiency (formula adjusted to 50%, Optia)
- Platelet sparing
- Flexibility of the COBE Spectra and CS3000 is less with successors
- Donor/patient safety are improved

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References

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