FDA evaluation of red cell products

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FDA reviews red cell transfusion products in conjunction with

- **Devices**
  - that collect or process RBCs for transfusion
  - *Regulatory pathway*: traditional or de novo 510k, PMA

- **Drug solutions**
  - for collection, processing and storage for RBCs
  - *Regulatory pathway*: NDA, ANDA

- **Manufactured RBCs**
  - *Regulatory pathway*: BLA
Device-related red cell review

• Apheresis instruments, automatic whole blood separators, leukoreduction filters, blood warmers,

• Red cells are the output of the device and are evaluated for their quality after collection, processing and storage.

• Risk based device review: Class II and Class III
  – Class II moderate risk- traditional or de novo 510k,
  – Class III high risk- Pre market approval (PMA)

• When the device is approved/cleared for US market, blood collection centers that distribute products in interstate commerce must obtain licenses to produce RBCs
Drug-related red cell review

• as part of a drug application for a blood collection and storage system-
• tubing, needles, bags, leukoreduction filters, drug solution
• Intended use: collection, processing and storage of red cells
• Drugs: Anticoagulants. Additive solutions
• Approved through NDAs and ANDAs
Manufactured red cells and “substitutes”

• Stem cell-derived RBCs, hemoglobin-based oxygen carriers,

• Large scale production, good manufacturing practice, quality controls

• Manufacturers will obtain biologic license application (BLA) to manufacture
Range of red cell products reviewed

- **Conventional red cells for transfusion**
  - manual collection and processing with approved anticoagulants into approved storage bags and with approved additive solutions
  - stored at cold temperatures up to 42 days post collection.

- **Slightly modified collection and/or storage process**
  - apheresis instruments collected RBC (same technology and intended use)
  - new storage bags,
  - new additive solution,
  - new leukoreduction filters

- **Significantly altered or synthesized red cells**
  - chemically treated for pathogen reduction,
  - ex vivo stem cell derived RBCs
  - extended storage or storage under unusual conditions
Recommended testing depends on the differences between a standard red cell and the new red cell product

<table>
<thead>
<tr>
<th>Extent of differences compared to conventional RBC product</th>
<th>In vitro studies</th>
<th>Phase I/II clinical trials</th>
<th>Phase III clinical trials for safety and efficacy</th>
</tr>
</thead>
</table>
| Minor  
• Minor changes to additive solution  
• Alternate supplier of raw material | ![Red cell](https://via.placeholder.com/150) | ![Red cell](https://via.placeholder.com/150) | ![Red cell](https://via.placeholder.com/150) |
| Moderate  
• New additive solution,  
• New devices for  
  - collection (apheresis)  
  - processing (filter)  
  - storage (bags) | ![Red cell](https://via.placeholder.com/150) ![Red cell](https://via.placeholder.com/150) | ![Red cell](https://via.placeholder.com/150) ![Red cell](https://via.placeholder.com/150) | ![Red cell](https://via.placeholder.com/150) ![Red cell](https://via.placeholder.com/150) |
| Significant  
• Pathogen reduced,  
• Extended storage beyond 42 days  
• Novel products (RBC substitutes, stem RBCs, | ![Red cell](https://via.placeholder.com/150) ![Red cell](https://via.placeholder.com/150) ![Red cell](https://via.placeholder.com/150) ![Red cell](https://via.placeholder.com/150) | ![Red cell](https://via.placeholder.com/150) ![Red cell](https://via.placeholder.com/150) ![Red cell](https://via.placeholder.com/150) | ![Red cell](https://via.placeholder.com/150) ![Red cell](https://via.placeholder.com/150) ![Red cell](https://via.placeholder.com/150) |

*In vitro* studies: Morphology, Biochemistry, Hemolysis
*In vivo* radiolabeling studies (kinetics)
**In vitro** studies for investigational and control red cell products

- Studies performed at two independent laboratories (Day 0 and day of expiration)
- Cell counts (RBC, WBC, Platelets)
  - Product weight, volume, hematocrit,
  - Leukoreduced products $< 5 \times 10^6$ WBC/unit
- RBC morphology, mean corpuscular volume (MCV)
- Biochemistry (ATP, 2,3 DPG, glucose, lactate, pH, $pO_2$, $pCO_2$)
- Concentrations of free and total hemoglobin,
  - level of hemolysis at $\leq 1\%$ at expiration
- Post device processing (i.e. leukocyte filtration) recovery $\geq 85\%$
- Post frozen/thawed/washed RBC mass recovery $\geq 80\%$
- Post rejuvenation RBC mass recovery $\geq 80\%$
Statistical considerations for *In vitro* studies

- Tests with a defined standard (i.e. \( < 5 \times 10^6 \) WBC/per unit)
  - 95% confidence that 95% of products meet specifications (95-95)
  - Success = 60 consecutive products with no failures (can pre-specify a larger data set that will allow failures i.e. 1/93, 2/126, etc.)

- Test without a defined standard (i.e. ATP levels, glucose, lactate)
  - Comparison to a conventional RBC product (red cell unit collected by approved methods and equipment)
  - Success = <20 % control difference between values from test RBC vs control RBC, 95% confidence that 95% of comparisons are within 20%

**Origin of 95-95 rule:** Draft Guidance for Industry Pre-Storage Leukocyte Reduction of Whole Blood and Blood Components Intended for Transfusion, January 2001

“... to use statistical methods for quality control testing in monitoring the leukocyte reduction process, to assure with 95% confidence that at least *(greater than)* 95% of the products meet intended product specifications.”
Clinical studies: *In vivo* 24 hr recovery of transfused autologous radiolabelled red cells

- Performed under IND or IDE
- 20-24 healthy volunteers
- At least 2 test laboratories independent from sponsor
- Sample mean in vivo recovery at 24 hrs ≥75%
- Sample SD ≤ 9%
- One-sided lower confidence limit for the proportion of RBC components with 24 hr RBC in vivo recovery >75% is 70%†
  †Allows for low recoveries (<75%) in 2/20 or 3/24 volunteers

- A control arm for the study using autologous FDA approved RBC products is recommended, but not required, to identify volunteers with naturally low RBC recoveries
## Historic development of the statistical basis of \textit{in vivo} rbc radiolabelled studies

<table>
<thead>
<tr>
<th>Period</th>
<th>FDA acceptance criteria for RBC products \textit{in vivo} study</th>
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<tbody>
<tr>
<td>~1997</td>
<td>75% RBC survival</td>
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</table>
| 1998~2003   | Mean RBC survival $\geq 75\%$  
Standard deviation $\leq 9\%$  
At least 20 volunteers at 2 sites                                                             |
| 2004~       | One sided lower 95\% CI for the population proportion of successes $> 70\%$  
(A success: RBC survival $\geq 75\%$)                                                     |
Proportion of studies that met the 95-70 criterion for *in vivo* radiolabelling studies from 1990-2007

(Jessica Kim, PhD, BPAC 2008 presentation)

Horizontal line (.875) indicates point estimate of studies that meet the 95-70 rule. (recoveries of higher than 75% in ≥21 out of 24 volunteers). The corresponding one-sided 95% confidence interval is 0.70 to 0.97 which sets the lower limit for a population at 70% (95-70 rule)
Additional studies for extensively processed novel RBC products

• RBCs chemically treated, extended storage, manufactured

• **Concerns about potential toxicity and efficacy issues:**
  immunogenicity, reduced cell flexibility, increased fragility, low oxygen delivery capacity, unanticipated toxicities

Studies to address these issues

• **In vitro**
  • Oxygen dissociation curves
  • Potential for 2,3 DPG regeneration
  • Immunogenicity

• **Clinical**
  • Immunogenicity/antibody formation monitoring
  • Phase 3 clinical trial for safety and efficacy compared to conventional red cell products
  • Phase 4 post market safety study
FDA determination of red cell quality - summary

• Evaluation process is based on extent of differences between a new product and a conventional product.
  – Highly different products get more scrutiny
• Tests include *in vitro* biochemical parameters and *in vivo* clinical radiolabelling studies for moderately different red cell products
• Significantly different products will likely need additional tests to evaluate RBC function (oxygen delivery) and safety in vivo (animal models, clinical trials)
FDA red cell review process-needed improvements

• Current process is designed to evaluate red cell products that are similar to conventional red cell products-
  – need to expand process to better evaluate very novel RBC products

• *In vitro* studies are not predictive of clinical performance-
  – need better pre-clinical tests that correlate with clinical outcomes

• *In vivo* studies are focused on red cell kinetics in circulation but not on oxygen delivery
  – need pre-clinical and clinical methods to evaluate oxygen delivery (in vitro tests and validated animal models)