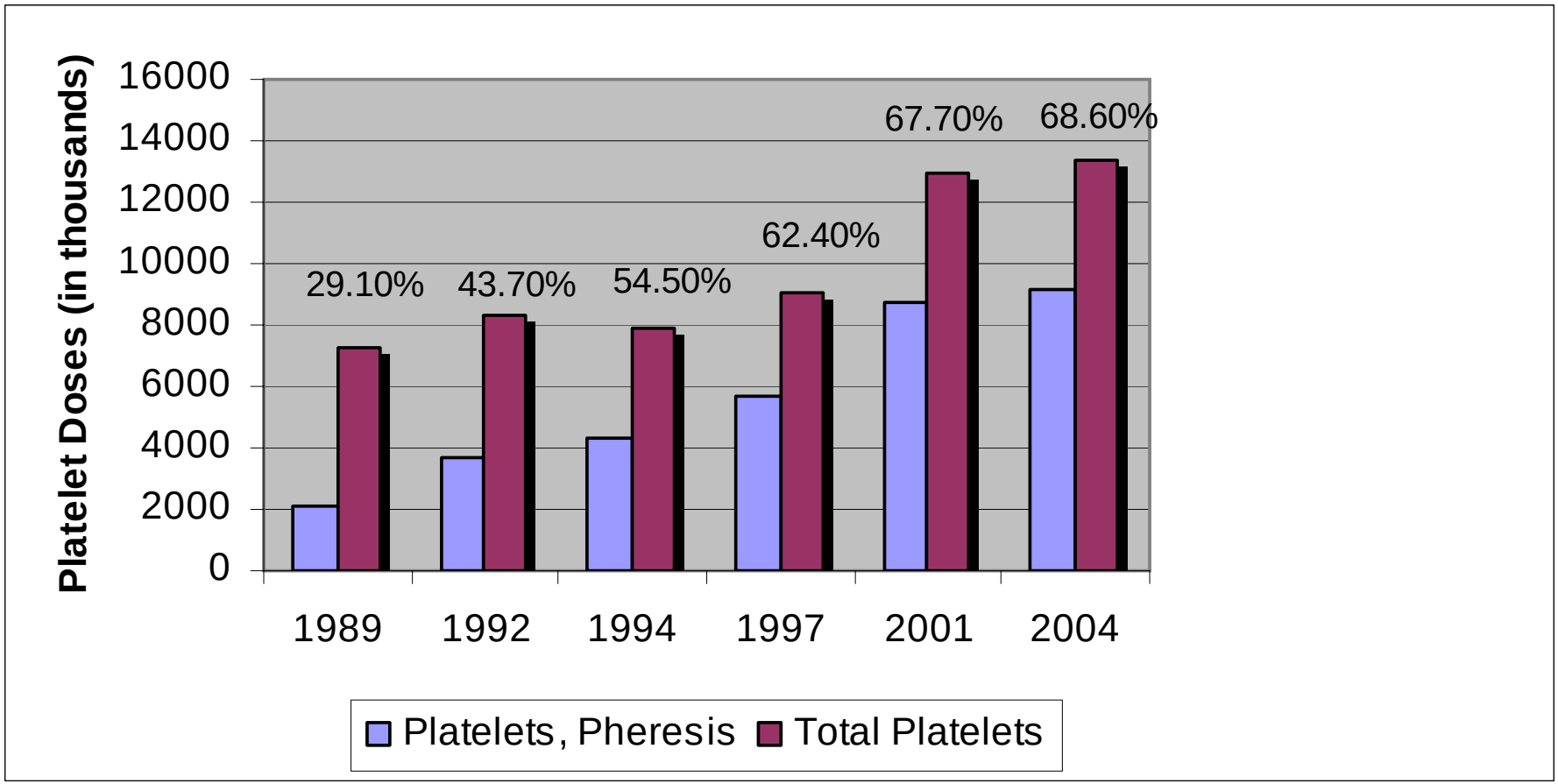
Licensure of Apheresis Blood Products

The Regulatory Paradigm and Managed Review

Increasing Proportion of Platelets, Pheresis Transfused 1989 – 2004 (NBCUS data)



License Supplements Received to date in 2007
OBRR Division of Blood Applications

Supplement	Total	Apheresis -Related
Prior Approval	314	45 (14 %)
CBE-30	120	53 (44%)
All	481	98 (20%)

Licensing of Blood Products

- Authority for Licensing Blood Products
- Biologics Licensing Regulations
- Biologics Licenses
- Significance of Licensing
- Changes to an Approved Application
- Alternative Procedures

Authority for Licensing Blood Products

- Public Health Service Act (Section 351(a))
  - License Required for Shipment in Interstate Commerce
  - License Required for Shipment into/out of the U.S.

Authority for Licensing Blood Products

- Federal Food, Drug, and Cosmetic Act
  - Requires registration of drug/device manufacturers (section 510)
  - Prohibits adulteration (section 501) and misbranding (section 502)

Biologics Licensing Regulations

- Title 21, Code of Federal Regulations
  - Parts 600, 601 – General Licensing Requirements
  - Parts 606 and 211 - Current Good Manufacturing Practice
  - Parts 610 – Labeling
  - Parts 630 – 660 – Additional Standards

Biologics Licenses
21 CFR 601.2

- To obtain a biologics license under section 351 of the Public Health Service Act for any biological product, the manufacturer shall submit an application to the Director, Center for Biologics Evaluation and Research …on forms prescribed for such purposes, and shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency… A full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product for introduction or delivery for introduction into interstate commerce; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); specimens of the labels, enclosures, and containers… and the address of each location involved in the manufacture of the biological product shall be listed in the biologics license application…

Biologics Licenses
21 CFR 601.2

- Establishment
  - Facilities
  - Responsible Personnel
  - Compliance

Biologics Licenses
21 CFR 601.2

- Biologics (Product) License Application
  - Separate Application for Each Product
  - Separate Application for Each Operating Location
  - Manufacturing Methods
  - Labeling
  - Products
  - Safety/Efficacy Data (if new product)

Significance of Licensing

- Signifies Approval
  - License number must appear on approved products
- Allows Interstate Shipment

Changes to an Approved Application

21 CFR 601.12

As provided by this section, an applicant must inform the Food and Drug Administration (FDA) about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved license application(s).

Changes to an Approved Application

- Reporting changes to an application are classified by the extent of the manufacturing change
  - Prior approval supplement (PAS)
  - Changes being effective in 30 days (CBE 30)
  - Changes being effective immediately (CBE)
  - Annual Report (AR)

Changes to an Approved Application

21 CFR 601.12 (b) Prior Approval Supplement (PAS)

Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes). A supplement shall be submitted for any change in the product, production process, quality controls, equipment, facilities, or responsible personnel that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

Changes to an Approved Application PAS

For a change under the PAS category, you must submit a supplement to your approved license application that includes the following:

- a detailed description of the proposed change;
- the products involved;
- the manufacturing site(s) or area(s) affected;
- a description of the methods used and studies performed to evaluate the effect of the change on the product's safety or effectiveness;
- the data derived from those studies;
- relevant validation protocols and data;
- appropriate labels; and
- relevant standard operating procedure(s) (SOP) or a list referencing previously approved relevant SOP.

Changes to an Approved Application PAS

We consider the examples below to be major changes, for which submission and approval of a supplement prior to distribution of product made using the change must occur:

- Product Manufacturing/Procedural Changes
  - Implementation of a new manufacturing process, to include but not be limited to:
  - Addition or revision of SOP s if the change is *less* restrictive than previously approved or is not addressed in published FDA guidance documents
  - Change from manufacturing a sole product by automated apheresis to manufacturing additional products as by-products. Request to manufacture additional products
  - Request for approval of a comparability protocol.

Changes to an Approved Application PAS

- Equipment Changes
  - Conversion from manual to automated collection of blood components; e.g., Platelets, Plasma (both Fresh Frozen and Source), Red Blood Cells, Source Leukocytes.

  - Changes or upgrades in automated apheresis equipment that affect the purity, potency or quality of the product(s). These changes include but are not limited to: increase in product yield; change in storage conditions; change in anticoagulant; leukocyte reduction; collection of an additional or different product.

  - Change in manufacturer of automated apheresis equipment used in the collection of Red Blood Cells or Platelets

Changes to an Approved Application CBE-30

21 CFR 601.12 (c)

Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change. A supplement shall be submitted for any change in the product, production process, quality controls, equipment, facilities, or responsible personnel that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.

Changes to an Approved Application

The requirements for the content of CBE30 supplements are the same as for PAS.

Changes to an Approved Application

We consider the examples below to be moderate changes, for which submission of a supplement at least 30 days prior to the distribution of the product made using the change should occur:

- Product Manufacturing/Procedural Changes
  - Addition of the collection of plasma as a by-product in an approved plateletpheresis program, provided the applicant is otherwise approved to manufacture the plasma product.
  - Request for an alternative procedure under 21 CFR 640.120 for which published guidance is available and implementation conforms with the guidance
  - Implementation of recommendations described in FDA guidance documents, if followed *without* modifications and directed to be reported in this manner by the guidance document.

Changes to an Approved Application

21 CFR 601.12 (c)(5)

In certain circumstances, FDA may determine that, based on experience with a particular type of change … the product made using the change may be distributed immediately upon receipt of the supplement by FDA. These circumstances may include substantial similarity with a type of change regularly involving a "Supplement--Changes Being Effected" supplement or a situation in which the applicant presents evidence that the proposed change has been validated in accordance with an approved protocol

Changes to an Approved Application

We recommend that you have a mechanism to track the date we received your CBE submission.

Changes to an Approved Application

We consider the following examples to be moderate changes that could be implemented at the time we receive your supplement:

Product Manufacturing/Procedural Changes

- Implementation of another manufacturer's previously approved SOP, with written permission from the manufacturer.
- Implementation of recommendations described in final FDA guidance documents, if followed *without* modifications and directed to be reported in this manner by the guidance document.

Changes to an Approved Application

21 CFR 601.12(d)

Changes to be described in an annual report (minor changes). Changes in the product, production process, quality controls, equipment, facilities, or responsible personnel that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product shall be documented by the applicant in an annual report

Changes to an Approved Application

Under 21 CFR 601.12(d), you must document changes to the product, production process, quality controls, equipment, or facilities, that have minimal potential to have an adverse effect on the safety or effectiveness of the product in an annual report. You must include a list of all licensed products involved, and a full description of the manufacturing and controls changes including: the manufacturing site(s) or area(s) involved, the date each change was made, and a cross-reference to relevant validation protocol(s) and/or approved SOP in your annual report.

Changes to an Approved Application

We consider the following examples to be minor changes, to be reported in an annual report:

- Product Manufacturing/Procedural Changes
  - Revision of SOP for the following categories if the change is *more* restrictive than previously approved or is not described in published FDA guidance documents
  - Change in the quality control method if the procedure is consistent with the manufacturer's directions.
- Equipment Changes
  - Changes or upgrades by the device manufacturer of automated apheresis equipment that does not affect the purity, potency or quality of the product(s), if the facility is already approved for the original procedure
  - Use of sterile connecting (docking) device to manipulate product in a sterile manner if approved to manufacture the product and use of the device is consistent with manufacturer's directions.

Changes to an Approved Application

A list of all the current recommendations for the reporting categories of changes to an approved application are documented in the FDA guidance document:

Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture, July 2001

http://www.fda.gov/cber/gdlns/bldchanges.htm

Changes to an Approved Application

If your manufacturing change is not in the regulations or guidance document, please contact your consumer safety officer.

Alternative Procedures

21 CFR 640.120

The Director, Center for Biologics Evaluation and Research, may approve an exception or alternative to any requirement in subchapter F of chapter I of title 21 of the Code of Federal Regulations regarding blood, blood components, or blood products. Requests for such exceptions or alternatives shall ordinarily be in writing. Licensed establishments shall submit such requests in accordance with 601.12 of this chapter.

Alternative Procedures

A list of previously approved alternate procedures can be obtained on the FDA web sites:

www.fda.gov/cber/blood/exceptions.htm

The Managed Review Process

- Description of the program
- How does it apply to blood establishments

Managed Review

- The Biologic's Program implemented a *Managed Review Process* to ensure that the PDUFA performance goals are achieved. This process establishes timeframes for specific review events so that managers can obtain current status of application review and to ensure that goals are met. The current process covers licensing submissions and is initiated by a request from industry for a pre-pivotal trial meeting. The process ends with the licensure of the biological product. The process has been so successful that management has extended the Managed Review Process to include non-PDUFA applications. The full implementation of the Managed Review Process will make the application review process more efficient and speed the review of applications.

Managed Review

FDA will also extend its current blood oversight, and regulation revitalization and reinvention project. The major areas to be addressed include: development of the BLA as it applies to blood establishments; development of Agency-wide goals and direction; coordination of Agency-wide resources to protect the blood supply; and the revitalization and rewrite of blood regulations.

Managed Review

- FDA also continues to improve efficiency of its review process by its automation initiative. The Agency is in the process of transitioning from a largely paper-based regulatory submission and review environment to an electronic environment.

Managed Review

Goal:

Review and act on 85% of complete blood bank and source plasma BLA submissions, and 90 percent of BLA supplements within 12 months after submission date.

Managed Review

The process incorporates into the review process：

- Milestones to ensure comprehensive and timely review
  - Mid-cycle
  - T-10
- Reviewer and supervisor accountability
- Timely final actions
- Quality Assurance

Contacts

Division of Blood Applications

(or your CSO)

OBRR/CBER/FDA

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