

# Regulatory Oversight & Feedback in Biotech Development

- ♦ Anticipating Regulatory Questions & Issues
- ♦ Regulatory & Development Considerations for Product Classes
  - Blood, Blood Components, & Blood Derivatives
    - Whole Blood, Platelets, and Special Blood Derivatives
    - Plasma Derivatives: IGIV, Albumin, Factor VIII, Fibrin Glue
    - Recombinant Factor VIII Issues: Kogenate, Recombinate, & ReFacto
  - Vaccines
  - Therapeutic Proteins: Monoclonal Antibodies
  - Allergens: Patch Tests & Extracts
  - rDNA-derived Rxs vs. Naturally-derived Rxs: Development Issues
  - Gene Therapy and Cell Therapy (covered separately in another presentation)
- ♦ Potential Hazards
- ♦ Biotech Disasters and Historical Milestones
- ♦ Manufacturing & Process Changes: Timing & Implications
- ♦ Patents: US & International Aspects
- ♦ Summary

This presentation is an overview of what catastrophes the regulatory authorities have as an historical record. If you are sensitive to the experiences that have preceded your product - for that product class - then you can better anticipate what types of issues the regulatory officials will scrutinize. Thus, a product by product evaluation is needed, since some areas won't apply to others.

The timing and impact of manufacturing/ process changes can vary greatly depending on the amount of structure-activity relationship data you have, product complexity, and the overall transparency of a comparability exercise. Even when additional studies are needed, the regulatory reviewers may give you greater latitude for doing some studies in parallel with clinical trials - when the existing SAR and comparability data are supportive. Otherwise, you may find it necessary to perform some studies as a prerequisite to clinical phases.

Patents: While patents are normally outside the deliberation of the regulatory bodies, the determination of whether a patent is valid or not can have tremendous impact on regulatory review and approval. In the US, a great many generic applications are delayed or complicated by patent litigation - sometimes frivolous on the part of the innovator.

Other Sources of Regulatory Feedback: Team Biologics Inspections (see **Attachment 3** of this section), Warning Letters (see **Attachment 2** of this section), FDA Presentations & Symposia

## Anticipating Regulatory Questions & Issues

- ♦ Need to anticipate regulatory questions and issues by studying:
  - product class,
  - history of relevant approved products and their development plans,
  - current state of the art for clinical assessment & surrogate endpoints,
  - Warning Letters for manufacturers of that product class,
  - Team Biologics inspection findings, and
  - FDA presentations and symposia related to your product.
- ♦ What are the general areas of concern regarding your product, process, or aspects of demonstrating comparability?
- ♦ Given process changes are inevitable, what are the best times to implement those changes and what's the impact on existing preclinical and clinical data - especially if comparability is difficult to show or conclude definitively?
- ♦ What additional data (e.g., development, characterization, etc.) might be needed as 'back pocket' slides to support your argument?
- ♦ When regulatory authorities require additional physico-chemical or preclinical information, how can you best negotiate performing these in parallel vs. rate-limiting studies?
- ♦ How can you avoid doing 'academic' studies for FDA and EMEA vs. studies that bear on clinically significant issues?

Depending on the product class you're reviewing, you will find a trove of information in Summary Basis of Approvals (by FDA), European Product Assessment Reports (EPARS) (by EMEA), patent searches, Web site searches, protein database banks, litigation records, company SEC (Securities and Exchange Commission) reports, Compliance Policy Guides, etc.

Prior to contacting FDA with any pre-IND submissions or other formal exchanges, the firm should have all of the background data in hand and compiled for easy reference or incorporation into your meeting packet.

When requesting meetings with FDA, the rule is to ask very specific questions so that they can offer up salient advice. The old approach of an information packet and a "What do you think?" ... doesn't go very far anymore.

It may also help to do some background checks on the FDA personnel that will be reviewing your product. If you see lots of immunologists, chances are you're going to have some considerable feedback on immunogenicity.

## Blood, Blood Components, and Blood Derivatives

- ◆ Following the AIDS epidemic in the 1980s from contaminated blood supply, the Red Cross was placed under Consent Decree (which is currently still in effect) by the FDA and required to implement cGMPs for operations. In 1997, FDA enacted a **Blood Action Plan** that focused on key compliance areas, such as:
  - improved donor screening and suitability regarding 'high-risk activity,' BSE/TSE exposure, or other behavioral aspects that boost exposure to infectious disease
  - validation of computer tracking systems for blood establishments
  - "look-back" features of contaminated units ("cradle-to-grave" accountability)
  - PCR testing of individual units and plasma pools
  - viral inactivation/validation for manufacturing (e.g., solvent-detergent treatment)
  - enhanced scrutiny and reporting of production errors and accidents
  - regulatory relief for post-approval changes to an approved application
  - Team Biologics inspections with dedicated inspectors for improved consistency across industry
- ◆ Most recent focus has been on donor screening for potential BSE/TSE exposure, West Nile Virus, and TRALI (Transfusion-related Acute Lung Injury).

Key FDA Publications Regarding Blood, Blood Components, and Blood Derivatives include:

Requirements for Blood, Blood Components, and Source Plasma; Final Rule - **8/6/2001**

Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents - **6/11/2001**

General Requirements for Blood, Blood Components, and Blood Derivatives; Donor Notification - **6/11/2001**

Requirements for Licensed Anti-Human Globulin and Blood Grouping Reagents; Final Rule - **12/12/2000**

Requirements for Licensed Anti-Human Globulin and Blood Grouping Reagents; Companion to Direct Final Rule - **12/12/2000**

Current Good Manufacturing Practice for Blood and Blood Components; Notification of Consignees and Transfusion Recipients Receiving Blood and Blood Components at Increased Risk of Transmitting HCV Infection ("Look back"); Proposed Rule - **11/16/2000**

Biological Products: Reporting of Biological Product Deviations in Manufacturing; Final Rule - **11/7/2000**

Requirements for Albumin (Human), Plasma Protein Fraction (Human) and Immune Globulin (Human); Final Rule - **8/28/2000**

## Whole Blood, Platelets, and Special Blood Derivatives

- ♦ Regulatory requirements for Whole blood, RBCs, Platelets, Recovered Plasma, Cryoprecipitated Antihemophilic Factor (AHF), Source Plasma, and Plasma Protein Fraction (PPF) are detailed under 21 CFR Parts, 600, 606, 607, 610, and 640.
- ♦ Blood collection centers are licensed individually. Key compliance problems are:
  - Poor or inconsistent donor screening and suitability testing regarding 'high-risk activity,' BSE/TSE exposure, or other behavioral aspects that boost exposure to infectious disease
  - Inadequate validation of computer tracking systems or lack of change control
  - Poor "look-back" features for contaminated units
  - Inconsistent testing of individual units
  - Poor quality oversight for reporting production errors and accidents
- ♦ BSE/TSE: If potentially infected individual's whole blood is used, units are recalled. If units have been used, the recipients are notified and tested long-term. While there has been no documented case stemming from IGIV, a look-back that reveals contaminated units used in finished product (under your inventory control) can precipitate quarantine and destruction - but units on open market might not be recalled (as they were in the past).

**RBC:** whole blood collected in anticoagulant and centrifuged to separate RBCs from plasma; RBC is about 85% of the original volume of RBCs and less and  $5 \times 10^6$  leukocytes/unit; typical unit volume is 240-340 mL and a hematocrit  $< 0.80\text{L/L}$  (80%). RBCs first choice Rx for all patients with symptomatic deficit of oxygen-carrying capacity (e.g., blood loss, anemia); when used for exchange transfusion should be less than 7 days old.

**Platelets:** prepared from a random unit of whole blood collected in CP2D anticoagulant solution and filtered to remove leukocytes - then suspended in small portion of original plasma; unit contains at least  $55 \times 10^9$  platelets suspended in 60 mL of plasma. Trace amounts of RBCs can be present, allowing color to range from pink to salmon. After filtration, platelets will have  $< 8.3 \times 10^5$  leukocytes/unit. Platelets indicated for treatment of bleeding due to thrombocytopenia due to blood loss or chemotherapy; contraindicated in patients with Thrombotic Thrombocytopenic Purpura (TTP) or Idiopathic Thrombocytopenic Purpura (ITP) - unless the patient has a life-threatening hemorrhage.

**Fresh Frozen Plasma (FFP):** separated from whole blood and frozen within 8 hours of collection which contains a minimum of 0.7 IU/mL of Factor VIII and 150 mg of fibrinogen plus other labile coagulation factors (e.g., Factor V). Most FFP indications are addressed by other products, but can be used for massive transfusion where there is demonstrated deficiency of Factor VIII and V - otherwise Frozen Plasma is OK. FFP is also indicated in exchange transfusion in neonates. FFP contraindicated with a coagulopathy can be corrected more effectively with vitamin K, cryoprecipitated AHF, or Factor VIII concentrates. FFP has same infectious disease risks as whole blood. FFP is not used for volume expansion when saline; Lactated Ringer's Injection, USP; Albumin, USP; 10% Pentastarch - or other sterile expanders can be used instead.

**Cryosupernatant Plasma (CSP):** prepared by thawing FFP (between 1-6C) and centrifugation; plasma is separated from insoluble precipitate, harvested and frozen. Each CSP unit averages 160-200 mL volume; deficient in high molecular weight multimers of von Willebrand Factor (vWF) - which are found in Plasma and Cryoprecipitated AHF. CSP indicated as exchange fluid in treatment of TTP and Adult Hemolytic Uremic Syndrome (HUS), but contraindicated in Factor VIII replacement conditions.

**Cryoprecipitate (CP):** prepared by thawing FFP (between 1-6C) and centrifugation; supernatant plasma removed and insoluble cryoprecipitate is refrozen. CP is a source of coagulation factors (Factor VIII, Factor XIII, and von Willebrand Factor (AHF-vWFT) present, as well as fibrinogen and fibronectin. CP indicated as a source of fibrinogen and Factor XIII; may also be used for Factor VIII. CP contraindicated unless lab data indicates specific hemostatic defect. Also contraindicated since many specific factor concentrates (and recombinant versions) are available, which are manufactured with viral inactivation steps. However, CP can be used to manufacture fibrin glue (also a viral inactivated product).

## Plasma Derivatives: IGIV & Albumin

- ♦ Regulatory requirements for plasma derivatives are detailed under 21 CFR Parts, 600, 606, 607, 610, and 640.
- ♦ **IGIV:** Regulators focus on Source Plasma screening and testing, plasma pool testing, process validation parameters, and viral inactivation/removal validation. Given the 40-year history of clinical use, FDA requirements for BLA are usually a small open-label study.
- ♦ **Albumin:** Although not a 'generic', FDA does not require clinical studies for albumin - only pharmacokinetic/pharmacodynamic (PK/PD) studies needed. Viral validation typically wasn't required as of 1995, but this may have changed. Production processes usually include heating for several hours.
- ♦ Key compliance problems are:
  - Poor or inconsistent donor screening and suitability testing regarding 'high-risk activity,' BSE/TSE exposure, or other behavioral aspects that boost exposure to infectious disease
  - Inadequate validation of computer systems or lack of change control
  - Poor "look-back" features for contaminated units
  - Inconsistent testing of individual units
  - Poor quality oversight for reporting production errors and accidents

Given the shrinking donor population, access to Source Plasma is reduced and costs are going up. A key aspect of the plasma derivatives marketplace is the commerce of fractionation intermediates (e.g., Fraction II paste, Fraction I+II+III paste, etc.) to other companies. However, demonstrating comparability of these fractionation intermediates is an involved - and not always successful - practice. A recent PPTA (Plasma Protein Therapeutics Association)-FDA workshop (May 2002) reviewed the comparability issues. Summary notes of the workshop - as well as transcripts of the meeting - are included in the CD ROM (Library - Blood and Source Plasma Regs folder).

Plasma pools are complex mixtures and minor production changes can have significant impact on safety or efficacy. Excipients like sucrose can impact via renal failure; aggregates can increase; immunoglobulin classes can shift; pH changes can impact stability of intermediates (e.g., fragmentation observed at pH 5.1 but stable at pH 5.4); source plasma freezing time (if frozen quickly, there is less activation of enzymes associated with vasoactivity); Prekallikrein activator (PKA) is a known contaminant with hypotensive effects, which were related to increased stirring times.

A particular complication is analytical test methods. Compendial test methods are often insufficient to satisfy the 'state-of-the-art' mandate, but often FDA won't allow firms to drop the compendial testing in lieu of more elegant methods; thus, manufacturer's are often required to do both for an indefinite period. Also, comparison of your product profile to another marketed product doesn't mean anything to FDA in terms of supportive data. However, if a competitor's product is associated with an adverse event and they link that to a physico-chemical parameter (e.g., PKA and hypotension), FDA will require ALL manufacturers to trend and place specifications on their related products. In other words, FDA considers adverse events to apply to an entire class of products ... but physico-chemical comparability of one product to another is not considered supportive for comparability changes.

# Plasma Derivatives: Major Products from Fraction Pastes

- ♦ Typical Plasma Fractionation Process →
  - Cryoprecipitate: Factor VIII, fibrinogen, fibronectin
  - Fraction I Precipitate: IgM, fibrinogen, fibronectin
  - Fraction I Supernate: Albumin, alpha and beta globulins
  - Fraction II+III: gamma globulins (e.g., IgG) that yield IGIV products
- ♦ Given limited donor pools, there is lots of commerce of fraction pastes (e.g., Fraction II or Fraction I+II+III) as starting materials
  - Must show comparability of: donor practices, validated shipping, quality assurance, process controls, validation, finished product, and stability

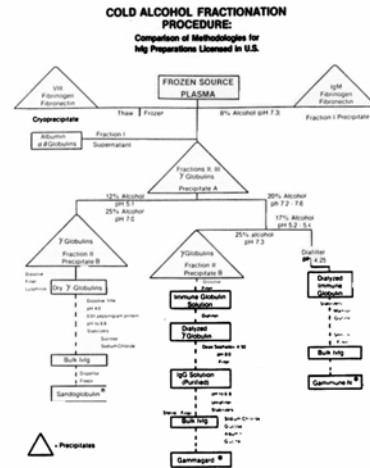


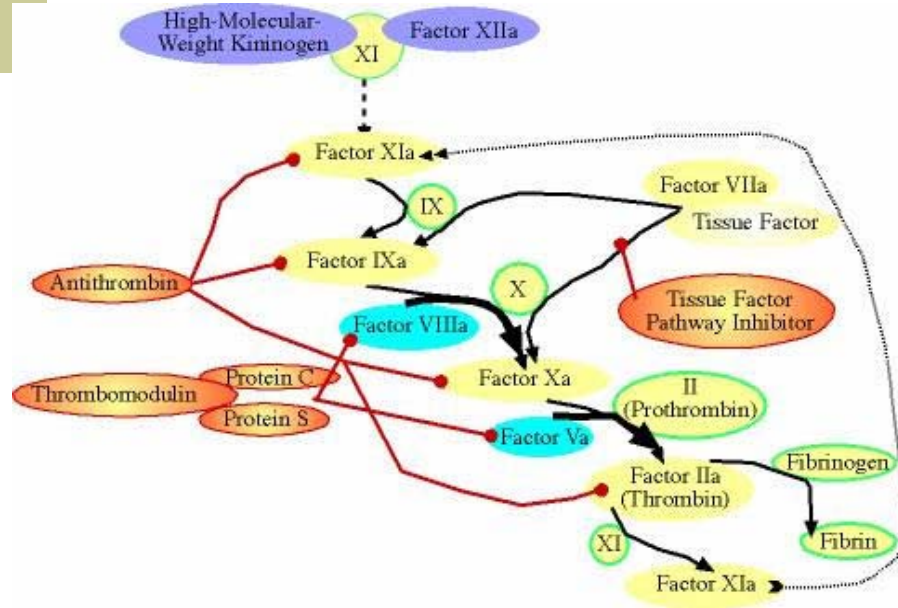
Figure 1-4. Cold alcohol fractionation procedure. Comparison of methodologies for IVIG preparations licensed in United States.

## Plasma Derivatives: Fibrin Glue

- As early as 1909, surgeons were reporting the hemostatic properties of fibrin powder used in the operative field. In the 1940s, combinations of fibrinogen and thrombin were first utilized. The development of Cohn fractionation in the 1940s, and a method for cryoprecipitation of fibrinogen in the 1960s, led to the development of fibrin sealants in the 1970s. However, fibrinogen concentrates were found to transmit hepatitis and thus all U.S. licenses for Fibrinogen (Human) were revoked 1997.
- Composition: typically comprised of thrombin and fibrinogen applied in a sterilized kit resembling a double-barreled syringe or gun to facilitate surgical application or sprayed on. When combined - thrombin activates fibrinogen to fibrin (clot formation). Products may also contain tranexamic acid, aprotinin or even factor XIII. Bovine glues have been discontinued
- Human plasma screened in the same manner as other plasma derivatives, but individual components are subjected to viral inactivation.
- Key indications: vascular surgery (e.g., liver, spleen) as well as dental surgery for hemophilia patients.
- Marketed Products: Beriplast (Aventis), Fibrin Sealant (Scottish National Blood Transfusion Service), a product by Omrix Biopharmaceuticals (offshoot of Octapharma) is in clinical trial

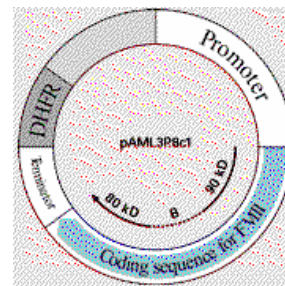
Human thrombin and human fibrinogen are applied separately to a bleeding site, and this results in the instant formation of a thin film of fibrin which controls the bleeding. It is important that the film is not swabbed away during surgery to maintain efficacy. The fibrin film will gradually be completely resorbed, with no resulting fibrosis at the site. Heat-treatment and solvent/detergent treatment are both used by different manufacturers. Furthermore, the efficacy of the products is further enhanced by inclusion of other substances in the glue or sealant which promote stability of the fibrin film.

# Schematic of Clotting Cascade



## Recombinant Factor VIII Issues: Kogenate

- ♦ Estimated number of hemophilia A patients is about 40,000 for US, Europe, and Japan
- ♦ Chief advantages of recombinant Factor VIII over plasma-derived derivatives are:
  - safety from HIV and hepatitis virus infection
  - product consistency and potency
- ♦ Disadvantages are high cost of goods: about 200 g per year. Also, potential contamination can result from mammalian MCB tissue cultures, downstream processing using immunoaffinity columns with antibodies from murine hybridomas, and contamination from stabilizers derived from human plasma (e.g., albumin) - such as is the case with Bayer's Kogenate
- ♦ Factor VIII is 2,232 amino acids - one of the largest ever produced in commercial biotechnology - as compared to insulin with 52 amino acids. Process development took 9 years.
- ♦ First-generation Kogenate was with human albumin formulation; second-generation material was albumin-free and formulated with sucrose



In 1984 the human factor VIII gene was first characterized (Gitschier, 1984). A DNA-fragment (cDNA) containing the nucleic acid sequences necessary for coding the factor VIII-protein was inserted in an expression vector. By applying biochemical methods the vector pAIVIL 3p.8c1, which carries the factor VIII gene was integrated into the chromosomes of the cells of a hamster kidney cell line (BHK). Cells that produced large amounts of the factor VIII protein were isolated and adapted to industrial production scale. The factor VIII producing R3-cell line which was derived this way was precisely characterized according to the inserted gene and its safety. Afterwards small aliquots of the cells were frozen in liquid nitrogen and stored as identical sources of cells for every Recombinant Factor VIII production campaign. The vector contains the regulatory sequences of a promoter and a terminator that enable the transcription of genetic information by the host cell. The dehydrofolate reductase gene (DHFR) serves the selection of transfected cells.

Regulatory review issues with recombinant clotting factors include: duration of biological activity, antigenicity and any impact on clinical safety and efficacy, viral validation, stability, etc.

## Recombinant Factor VIII Issues: Recombinate & ReFacto

### ♦ **Recombinate:**

- **Recombinate Efficacy:** Evaluated in 153 patients (65 previously-treated; 75 naïve patients; 13 surgical)
- **Recombinate Adverse Reactions:** AEs occasionally seen with factor concentrates are headache, fever, chills, flushing, nausea, and vomiting. Reactions noted in 13 out of 13,394 infusions during clinical trials. No serious reactions have been reported.

### ♦ **ReFacto:**

- recombinant factor VIII product formulated without the addition of human serum albumin in its final formulation
- Safety profile comparable to other Factor VIII products
- 20% of patients develop neutralizing antibodies

#### •Recombinate

**EFFICACY** - Altogether over 21 million units were infused. Bleeding in joints and soft tissues was managed successfully. In surgical situations, hemostasis (the ability to stop bleeding) was maintained throughout the surgical period. **ADVERSE REACTIONS** - As Recombinate contains trace amounts of mouse, hamster and bovine protein, there is a remote possibility patients may become allergic to these non-human proteins. Signs of an allergic reaction are hives, rash, tightness of the chest, wheezing, low blood pressure and difficulty in breathing. If such a reaction happens, infusion should be stopped at once.

#### •ReFacto

ReFacto is a recombinant factor VIII product formulated without the addition of human serum albumin in its final formulation. In the European Union, ReFacto is indicated for the control and prevention of hemorrhagic episodes and for routine and surgical prophylaxis in patients with hemophilia A. The product received marketing authorization from the EC in 1999. The U.S. Food and Drug Administration approved ReFacto for marketing in 2000. During clinical trials, ReFacto had a safety profile comparable to other factor VIII products. As with the intravenous administration of any protein product, adverse reactions may include headache, fever, chills, flushing, nausea, vomiting, lethargy, or manifestations of allergic reactions. Although most individuals with hemophilia can use replacement products repeatedly without problems, about 20% develop neutralizing antibodies that make the product less effective. Antibody inhibitors are more likely to occur in individuals with severe hemophilia. At this time, it is not possible to predict who will develop the antibody inhibitors, but there is some evidence for genetic predisposition for an immune response. The treatment for people with inhibitors can be complex and expensive. Often more than one approach is tried before the bleeding is arrested. The decreased ability to control bleeding in the joints can lead to earlier development of arthritis. In some cases, immune tolerance can be induced which allows standard treatment to again be effective. Studies are being conducted to avoid or modify the immune response and to prepare recombinant factor VIII proteins with reduced antigenicity.

# Vaccines

- ◆ Four major types: **viral** (live, killed, attenuated) vs. **bacterial, parasitic, & allergenic**  
Any vaccine may be composed of whole cells, purified components, and/or conjugated to other proteins such as diphtheria toxoid.
- ◆ Key aspects are:
  - Relationship of antigen epitope to observed seroprevalence associated with infection
  - Potential value of antibody profile in prevention or treatment of condition
  - Duration of antibody response and consistency of immunoglobulin profile
  - Characterization of antibody profile (e.g., binding, neutralizing, immunoglobulin subtype, etc.)
  - Vaccine specificity - as in no cross-sensitization or long-lived sequelae to other antigens; no cross-reactivity to normal human tissue.
- ◆ Other compliance issues include:
  - Thimerosal (mercurial) preservatives in vaccines: FDA is pushing for their removal
  - Comparability assessments for antigen shifts: How do you know the vaccine is still effective when there are subtle changes in immunological profile? HINT: Do old vaccinated patients' Abs recognize the new antigens?
  - Establishing efficacy when the use of humans is impossible, such as anthrax vaccine.

*Federal Register* Notice; Biological Products; Bacterial Vaccines and Related Biological Products; Revocation of Biologics Licenses - 5/29/2001

Draft Guidance for Industry: Post-marketing Safety Reporting for Human Drug and Biological Products Including Vaccines - 3/12/2001

Guidance for Reviewers: Potency Limits for Standardized Dust Mite and Grass Allergen Vaccines: A Revised Protocol - 11/20/2000

Draft Guidance for Industry: Considerations for Reproductive Toxicity Studies for Preventive Vaccines for Infectious Disease Indications - 9/8/2000

*Federal Register* Biological Products; Bacterial Vaccines and Related Biological Products; Implementation of Efficacy Review; Proposed Order - 5/15/2000

Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product - 1/5/1999

Guidance for Industry: How to Complete the Vaccine Adverse Reporting System Form (VAERS-1) - 9/8/1998

Guidance for Industry for the Evaluation of Combination Vaccines for Preventable Diseases: Production, Testing and Clinical Studies - 4/10/1997

Points to Consider on Plasmid DNA Vaccines for Preventive Infectious Disease Indications - 12/27/1996

## Vaccine Adverse Event Reporting System (VAERS)

A vaccine safety surveillance program co-sponsored by the FDA and the Centers for Disease Control and Prevention (CDC)

In the 1980s, a series of serious, life-threatening allergic/anaphylactic reactions to various vaccine proteins caused a number of vaccines to be withdrawn from the market. Numerous class action law suits followed and Childhood Vaccine Act of 1986 was established.

## Therapeutic Proteins: Monoclonal Antibodies

- ♦ Category includes blood derivatives, antitoxins, proteins generated by hybridoma or recombinant DNA technology (e.g., monoclonal antibodies, cytokines (e.g., interferon, interleukins), and tissue growth factors - as well as products from manipulated, cultured, or expanded human cells
- ♦ Monoclonal Antibodies: The largest class of biotech products under development; some 300 in IND stage but only a handful approved:
  - Herceptin (indicated for metastatic breast cancer); Rituxan (indicated for refractory non-Hodgkin's lymphoma); ReoPro (indicated for prevention of blood clotting during angioplasty); Remicade (indicated for Crohn's disease and rheumatoid arthritis); Oncoscint (indicated for colorectal cancer imaging)
  - Potency may be defined by specific activity; obviates complicated bioassays that require both binding and activation.
  - Safety issues: cross-reactivity with normal tissue; toxicity due to a conjugated toxin or radioactive particle; patient's immune response; impurities that may contaminate or infect the patient.
  - Comparability can be shown via: N-terminal sequencing, *in situ* CNBr sequencing, AAA, peptide mapping, MALDI-TOF, degradation pattern, DSC, SEC-HPLC, CE, SDS-PAGE, IEF, Western Blot, carbohydrate composition, carbohydrate profiles (glycosylation analysis)

Preclinical testing for MAb products may include: single and repeat dose tox studies, dependence study, local irritation, pyrogenicity, immunogenicity, general pharmacology, ADME, cross-reactivity, binding to target, and product stability. See *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use* for details on CMC and preclinical considerations.

## Allergens

- ◆ Two types of allergenic products: patch tests and extracts
- ◆ Patch Tests: diagnostic test applied to the skin to determine specific cause of contact dermatitis
- ◆ Allergenic extracts: used for diagnosis and treatment of allergic diseases such as allergic rhinitis ("hay fever"), allergic sinusitis, allergic conjunctivitis, bee venom allergy and food allergy
- ◆ Allergenic extracts are currently manufactured in two forms: standardized and unstandardized.
  - Prior to release standardized allergenic extracts are compared to US reference standards for potency. CBER maintains these reference standards and distributes them to manufacturers. There are currently 19 standardized allergenic extracts.
  - Extracts for which there are no US reference standards are called unstandardized extracts.

Patch tests are manufactured from natural substances or chemicals, such as nickel, rubber, and fragrance mixes, that are known to cause contact dermatitis. Allergenic extracts are injectable products that are manufactured from natural substances, such as molds, pollens, insect venoms, animal hair, and foods, known to elicit allergic reactions in susceptible individuals. Food extracts are only used to diagnose food allergies, but other allergenic extracts may be used for both diagnosis and treatment of allergic disease.

## rDNA-derived Rx's vs. Naturally-derived Rx's: Development Issues

- ♦ rDNA-derived Rx's have been approved for:
  - Insulin
  - Growth hormone
  - Factor VIII
  - Parathyroid hormone
  - Calcitonin
  - Albumin (see comments below)
  - Tissue plasminogen activator (tPA)
  - Urokinase
- ♦ FDA notes that drugs approved under Section 505(b)(1) of the FD&C Act can be approved via 505(b)(2) route (see October 2000 guidance)
- ♦ While CBER has no mechanism for recognizing any abbreviated pathway and publicly does not recognize any comparability data as a shortcut, the actions of approved products says different (e.g., Factor VIII).
- ♦ FDA says it routinely asks for a full development program, but often the actions say otherwise. If it's a 'drug' regulated by CDER, there can be significant savings on the preclinical side from reduced toxicology testing (e.g., PTH program)
- ♦ Even on the biologics side, recombinant blood derivatives (e.g., Factor VIII [Refacto]) were compared to native forms and allowed reduced testing by EMEA authorities.

**Albumin:** Comparing naturally-sourced plasma derivatives vs. recombinant plasma derivatives, the regulatory bodies routine require preclinical and clinical testing - as with any new biotech product. This point was brought out by Kaoru Kobayashi (Mitsubishi Pharmaceutical Corporation) Recombinant Human Serum Albumin. Dr. Kobayashi presented results of the development of a recombinant human albumin (at the ICH QE5 meeting on comparability). The product was compared to human albumin purified from serum by a number of analytical techniques and was shown to be very similar. However, it was recognized that this is a new molecule and therefore preclinical and clinical studies have been and are still performed in order to get regulatory approval.

**Insulin:** The FDA review and approval of Humulin (in 1982) was a record-breaking 5 months. The Agency felt that they could move rapidly because the product so closely matched the native insulin. The product was tested clinically in about 400 patients in 12 centers, but the intolerance to rDNA-insulin (vs. animal insulin) was not discovered until after post-approval.

**Parathyroid Hormone:** While personally working on a PTH project for osteoporosis, FDA noted that extensive toxicology studies were not needed given the physico-chemical comparability of the rDNA-derived product to the native protein. There was no discussion of immunogenicity either.

The bottom line is that as analytical methods improve, there can more confidence in the comparability studies of rDNA-derived vs. naturally-derived materials. This should obviate some preclinical testing, but that's not always a given. The approval standards used in 1980s and 1990s seem slight compared to today's scrutiny. However, if there is a compelling need for a product - as in blood and plasma derivatives - regulatory agencies will work with companies to fast track and have enhanced pharmacovigilance post-approval.

## Potential Hazards

- ◆ **Adventitious Agents**
  - Bacterial (endotoxins, host cell proteins, exotoxins, extraneous enzymes)
  - Viral (HIV; Hepatitis A, B, non-A/non-B, C; HTLV; polio; rubella, etc.)
  - Mycoplasma (Tuberculosis)
  - Prions (BSE/TSE)
  - Genetic Material (nucleic acid fragments from tissue cultures, modified genetic material from gene therapy, altered DNA expression for endogenous cells used in gene therapy, other proteins that might promote oncogenicity or mutagenesis.)
- ◆ **Chemical Contamination**
  - Antibiotics
  - Impurities (e.g., L-tryptophan crisis)
  - Pesticides (e.g., aminotriazole contamination of cranberry crop in 1959)
  - Heavy metals (e.g., arsenicals, mercury [thimerosal], etc.)
- ◆ **Drug-related Hypersensitivity**
  - Beta lactam ring antibiotics (e.g., penicillin, cephalosporins)
  - Acquired sensitization by particular patients
  - Immunogenicity (e.g., mild rashes ranging to anaphylaxis: Type I, II, III, or IV)
  - Anomalous (e.g., TRALI, PRCA, CIC deposition, autoimmune sequelae, etc.)

TRALI (transfusion related acute lung injury): observed in some patients receiving blood products with plasma resulting in a serious, life-threatening pulmonary syndrome. TRALI first reported in 1992 and now have more than 45 fatality reports on file. See accompanying letter from FDA to industry.

PCRA (platelet red cell aplasia): condition noted mostly with subcutaneous injections of Eprex formulation, but not much seen with Epogen IV or Epogen SC. FDA still investigating relationship of formulation and route of administration.

CIC (circulating immune complex): deposition of CIC in pulmonary beds can be overwhelming in strong allergic reactions and precipitate pulmonary crises (e.g., shortness of breath, anaphylaxis, etc.).

## Biotech Disasters & Historical Milestones

- ♦ Vaccines:
  - Diphtheria vaccine contamination (1902)
  - Polio vaccine contamination (1955)
  - German Measles (Rubella) outbreak and expedited vaccine development
  - Whooping Cough (pertussis): poor safety record led to acellular vaccine development in 1949
- ♦ Blood and Plasma derivatives:
  - AIDS spread unchecked through the blood supply until an HIV test kit was approved in 1985
  - Poor cGMP practices precipitated a huge recall of albumin, clotting factors, and test kits made with potentially septic material
  - Fractionated pastes: recalled due to suspected contamination by BSE/TSE
- ♦ Chemical:
  - L-tryptophan: impurity contamination caused 38 deaths and 1,500 confirmed cases of EMS (eosinophilia-myalgia syndrome)
- ♦ Abbokinase: major fibrinolytic used for keeping IV lines open was recalled for cGMP violations
- ♦ Gene Therapy & Tissue:
  - Cylolife - material recalled due to donor deaths and inadequate testing
  - Potential for transformed genetic material to alter patient response
  - Potential for transfer of adventitious agents via poor control of sterility and sourcing materials

For details of the above, see **Attachment 1 - Cautionary Tales of Biotech Production.**

## Manufacturing & Process Changes: Timing and Implications

- ♦ Types of Manufacturing/Process Changes
  - MCB (e.g., adherent to non-adherent strain, serum-free, expression system changes, etc.)
  - Fermentation (e.g., scale, duration, conditions, media, etc.)
  - Purification (e.g., addition/deletion of steps, reorganization of steps, change in filter quality or excipients, etc.)
  - Viral Validation (e.g., when to repeat given significant manufacturing changes?)
  - Sterilization (e.g., change in sterilizing filters, change in filtration conditions, etc.)
- ♦ Types of Analytical Changes
  - Purity/Impurities Methods (e.g., revised method, additional method, cross-over comparability)
  - Pesticides (e.g., aminotriazole contamination of cranberry crop in 1959)
  - Heavy metals (e.g., arsenicals, mercury [thimerosal], etc.)
- ♦ Comparability Assessment
  - What is phase of clinical trials? IND Phase I, II, III or post-BLA filing?
  - What critical SAR links have been made to avoid clinical bridging studies?
  - What preclinical studies might obviate clinical trials?
  - What is best timing for filing changes? Pre-Phase III, during BLA review, post-approval?

One of the most vexing aspects of biotech development is **when to implement significant manufacturing changes**. There are some advantages to keeping everything scaled-down through Phase III and the BLA filing to keep a project fast-tracked, but this means an enormous gamble of scale-up and comparability assessment while simultaneously defending the BLA under review or post-approval (as Bayer did with Kogenate or Genentech with Activase). If the comparability exercise doesn't work, then a lot of additional development and validation may need to be repeated prior to marketing. However, a number of firms like this approach ... get licensure based on product made at a pilot facility and then supplement the approved BLA with the scaled-up material from the new facility. If things go well, the switch can be seamless. If not, the company ends up with gaps in product availability (e.g., Enbrel for rheumatoid arthritis).

Other firms may adopt a parallel track; do the Phase III studies and BLA stability with one process scale and start scale-up before filing the BLA. If things go well, the comparability data should be ready while the BLA is still under review - or shortly after approval. While this approach saves time, it costs a lot. May not be practical for a small biotech firm with only one product and a limited 'burn rate' or capital resources. Recently, FDA issued a letter summarizing major problem areas with BLAs that had 'multiple review cycles.' See a copy of this in **Attachment 5 - FDA Comment on BLA Filings with Multiple Review Cycles**.

The more well-characterized the material and the better the SAR, the less likely you need to repeat clinical studies ... even with significant differences. For instance, Genentech developed tPA in a roller bottle and then scaled up to a non-adherent cell line (for microbeads) and saw differences in product profiles (predominantly single chain vs. double chain). They had to perform a small (15-30 patient) bridging study to get to market. However, Biogen's Avonex (beta interferon) was able to make the comparability assessment purely by physico-chemical data even after completely new cell lines.

Manufacturing/process changes are best controlled by the sponsor but that's not always the case. Anomalous deaths (e.g., gene therapy) or Team Biologics inspectional findings (done at PAI or post-approval) can force the company to implement a major Corrective Action Plan (CAP) that entails significant upgrades to HVAC, WFI, and equipment validation. The level of FDA oversight can dramatically impact costs and timing; the worse off the situation - the more FDA will ride you to quick compliance.

## Patents: US Aspects

- Patents are granted based on being (1) novel and (2) non-obvious
- Patent & Trademark Office (PTO) Requirement of Demonstrated Utility
  - For years, the PTO standard definition for 'utility' of a potential biotech treatment was demonstration of efficacy - successful clinical trials - before the patent was granted. In 1995, the PTO revised their criteria for demonstrating utility for treatment. However, where an invention makes a claim of a cure, the inventor must be prepared to demonstrate greater evidence of utility. The guidelines were meant to improve the quality of biotech patents and ease the requirements for demonstrating utility of a patent with therapeutic claims.
- Process Patent Act of 1998
  - expanded process protection to remedy situations where US patented processes were infringed upon outside of the US, but the resulting products were imported/sold in US.
  - held that parties responsible for import, use, or sale of US patented processes were liable for infringement
- Biotechnology Patent Protection Act (BPPA) of 1995
  - provided patent protection for an old process that is used to make a new and non-obvious product
- Bolar Provision (Hatch-Waxman Act of 1984): see explanation below

**Biotechnology Patent Protection Act (BPPA) of 1995:** This legislation was as a remedy following the 1985 Durden ruling in which a federal appeals court held that a process that used novel starting materials and produced a novel end product couldn't be patented unless the process was also novel. Until the BPPA, this ruling effectively limited a number of biotechnology advances and exposed the industry to competition from outside the US.

**Bolar Amendment:** This provision was part of the Drug Price Competition and Patent Extension Act of 1984 (also called Hatch-Waxman) that allowed generic firms to produce pharmaceuticals for development and registration purposes only - while the patent terms of the innovator were still in effect. Although hotly contested, this proviso has allowed drug development to commence much sooner than the innovator wanted - to the point of having several tentatively approved applications at FDA that are approved for marketing within a day or so of the patent expiration. NOTE: There is no Bolar provision for European firms such that any development must take place outside of the European market - since the production of material even for registration purposes is in violation of the data exclusivity regulations. Currently, the Bolar proviso is being proposed by generic firms as part of a harmonization of generic drug law and to help satisfy socialized medicine/formulary costs.

## Patents: US Aspects (continued)

- Festo v. Shoketsu Kinzoku Kogyo Kabushiki Co. (also known as SMC Corp.) (2002)
- In 1988, Festo sued FMC under the doctrine of equivalents regarding infringement of magnetic pneumatic tubes, which prevents one from taking a patented item by changing a few minor things.
- In Festo's case, a second patent law doctrine - prosecution history estoppel - came into play, which puts limits on what can be argued under the doctrine of equivalents.
- When a company first files a patent, there is a prosecution stage during which the firm defends the patent offices challenges to the claim. The company responds by amending the claim, usually narrowing its scope to satisfy the patent office. During this process, a patent may be modified several times to finally meet the patentability criteria.
- The doctrine of prosecution history estoppel argues that any change made through an amendment limiting the extent of the patent is binding and the company will not be able to argue later that the limit doesn't exist.
- In Festo, a lower court adhered to a rigid interpretation of the patent under the prosecution history estoppel - which would have made ALL patent claims subject to a much more narrow focus. Put another way, it would have rocked the world (and portfolios) of every major patent holder.
- However, the Supreme Court ruled the prosecution history estoppel was not effectively reducing the breadth of claims of the patent merely because they had not demonstrated ALL possibilities under the patent - that a representative demonstration was sufficient to show novel and non-obviousness.

As for Festo, the patent courts recently ruled on a major point regarding Doctrine of Equivalents. At issue is whether the courts should adhere to the literal wording in the final patent claims or be interpreted more broadly, as has been done historically. The Supreme Court recently ruled to keep the status quo (more broadly).

Had Festo been interpreted the other way, firms would have had to amend their patents with data from testing functional variants. What remains to be seen is that if a variant is not described in the first patent - but covered - can it be patented under a second patent where it is now explicitly described?

This is the heart of 'evergreening' in that a competitor may find itself challenged in court by the patent holder - claiming the infringement is covered under the undescribed art - but if that competitor never challenged it in the first place, would the variant now be the subject of a second patent? See **Attachment 6 - Festo Ruling** for details of the case.

## Patents: International Aspects

- Uruguay Round Agreement Act of 1994: *General Agreement on Tariffs and Trade (GATT)*
  - Previous 17-year patent term (from date of issue) was replaced by a 20-year term (from date of filing).
  - All applications filed before June 8, 1995 and those in effect as of June 8, 1995 have a term of 17 years from issuance or 20 years from filing, whichever is greater.
  - Term extension did not apply retroactively to patents expiring before June 8, 1995
- Doctrine of Equivalents: *Warner-Jenkinson Co. v. Hilton Davis Chemical Co., 117 S. Ct. 1040 (1997)*
  - Supreme Court ruled that an accused product or process is so similar to what's patented, it infringes by equivalence - though not literally. Doctrine of Equivalents prevents competitors market access by only slightly modifying patented processes
  - Requires infringement analysis (two step process) - determining the meaning and scope of patent claims allegedly infringed and determining whether the accused product/ method infringes on one or more claims. The Court's ruling by this determination differed from previous infringement test methods, such as the traditional "three-part-test" showing the claimed and accused products or processes perform substantially the same function, in substantially the same way, to produce substantially the same result. Other infringement test methods include assessment of interchangeability of products or processes.

### Uruguay Round Agreement Act of 1994 (General Agreement on Tariffs and Trade [GATT]):

**Continuation/ Divisional Applications:** Applications filed on June 8, 1995 or later will expire 20 years from U.S. filing of the earliest filed parent application. **Term extension:** A patent term can be extended up to 5 years if issuance of patent is delayed by an interference proceeding, a government secrecy order, or appeals to either the Board of Patent Appeals and Interferences or the Federal Circuit Court of Appeals.

**Provisional Patent Applications:** Provisional applications may be filed at a reduced fee rate; application need not contain claims but must be a full disclosure of invention. A complete application filed within 12 months can claim priority of the filing date of the provisional application, since the 20-year term is based on the filing date of the complete application. Provisional applications are automatically deemed abandoned after 12 months; not entitled to claim priority of the filing date of any other patent application.

**Foreign Activities to Prove Invention:** Effective January 1, 1996, inventors could rely on activities in WTO (World Trade Organization) countries - in addition to NAFTA countries - to prove a date of invention in proceedings in the PTO and courts. **Infringement:** Effective January 1, 1996, definition of infringement will be expanded to include not only making, using, and selling the patented invention, but also an offer for sale of the claimed invention or importation of the invention. Infringing activity must take place prior to the expiration of the patent. For situations where the term of an existing patent is extended beyond 17 years, persons who expended a 'substantial investment' before June 8, 1995 towards making or using that invention will be exempt from remedy provisions, but may continue after payment of equitable remuneration to the patent owner. NOTE: This 'delta period' was evaluated for 94 patents; courts ruled that filing an ANDA did not meet the 'substantial investment' criteria.

## Patents: International Aspects (continued)

- House of Lords Ruling: *Biogen v. Medeva PLC* (1997)
  - claims had been (1) for any recombinant DNA molecule that expressed the genes of any HBV antigen in any host and (2) for any method of making a DNA molecule that would achieve the necessary expression.
  - The court ruled on "not whether the claimed invention could deliver the goods, but whether the claims cover other ways in which they (the goods) might be delivered - ways which owe nothing to the teaching of the patent or any principle which it disclosed."
- Patents & Generics in Europe
  - Supplementary Protection Certificates (SPC) came into effect for EC in January 1993; effectively lengthened patents for products that would have expired in or after 1993 for the shorter of (1) an additional 5 years beyond the original 20 year term or (2) 15 years from first marketing authorization in Europe
  - SPC did not alter the law as to the "experimental" use exception from patent law - which is used in the US (under Bolar) for manufacturing development and registration lots

**Doctrine of Equivalents: Lords' "landmark" Patent Ruling (*Biogen v. Medeva*):** The court felt that there was more than one way in which the breadth of a claim could exceed the technical contribution to the art embodied in the invention. "The patent may claim results it does not enable - such as making a wide class of products when it enables only one of those products and discloses no principle which would enable others to be made. Or it may claim every way of achieving a result when it enables only one way and it is possible to envisage other ways of achieving that result which make no use of the invention."

**Patents & Generics in Europe:** The SPC did allow experimental exceptions when the intention of the study is to determine whether or not the material really works ... not a confirmatory study to demonstrate bioequivalence for registration purposes. However, recent court rulings (see **Attachment 6**) noted the definition of 'experimental' is subjective and could be interpreted differently - particularly for biotech products. For instance, if two companies have slightly different AA sequenced proteins that are covered under the same patent - but it's not a guarantee that they are both therapeutically equivalent, then one could argue the experimental proviso of the SPC and patent law should allow a multisource biotech approach - especially if firms are contending they should be performing the whole development program. If this is expanded, then a multisource approach could take place within Europe under the current data exclusivity provisions.

## Summary

- ♦ Anticipate the regulatory agency questions and issues by studying the product-specific nature of your project.
- ♦ Know the expertise of the reviewing division at FDA, Health Canada, EMEA, MCA, etc.
- ♦ Have extensive physico-chemical data with SAR (structure-activity relationship) links to your product - as well as demonstrations of previous product approvals on that basis. This will facilitate significant manufacturing changes.
- ♦ Use an experienced development team to handle CMC-analytical development engines so that they work in synchrony with clinical plans. You don't want a pivotal efficacy study done with pilot scale material (unless you plan to go to market with that process scale).
- ♦ Explore the details of the patents and potential litigation - at the very beginning - since that way you won't waste effort on projects with significant litigation or delays.
- ♦ Where there is doubt, take a less risky, more conservative route if you can afford the time and money. For instance, a potential loophole in the SPC and European patent law MIGHT allow you to do develop within the EC ... but if there is a chance not, best to take it elsewhere.
- ♦ Take advantage of existing medical markers and surrogate endpoints to make your case for clinical evaluation. For example, radioimaging and other diagnostic imaging allows for non-invasive measurements of joint erosion, cardiac perfusion, neurological stimulation, etc. These are much more amenable than extended clinical studies with simply laboratory values and morbidity rates.
- ♦ Reduce regulatory and legal risks by partnering with experienced, credible development teams (e.g., Merck, etc.) - which should help considerably with frivolous litigation and FDA-requested "academic" studies.