TEAM BIOLOGICS

A PLAN FOR REINVENTING FDA'S ABILITY TO OPTIMIZE COMPLIANCE OF REGULATED BIOLOGICS INDUSTRIES

I. Background - Needs to be Addressed

The Food and Drug Administration is a team of dedicated professionals working to protect, promote, and enhance the health of the American people. One of the most critical responsibilities of the Center for Biologics Evaluation and Research (CBER) is to ensure that biological products, including products derived through biotechnology, are safe and effective for their intended uses. CBER also assures that biological products do not provide a conduit for the transmission of infectious disease and are in full compliance with appropriate laws and regulations.

To remain an effective agent to protect the public health, FDA frequently assesses its internal procedures to identify emerging problems and trends and to determine if the risks associated with new products and technologies are being considered. Within the overall framework of the National Performance Review (NPR), FDA has assessed its policies, operations, training plans, and programs that relate to FDA's regulation of industries associated with the production of biological products. At the same time, recent oversight reviews by the Government Accounting Office and Institute of Medicine and inquires from the HHS Inspector General and Congress have raised concerns about FDA's regulatory oversight.

These factors have prompted FDA to establish a framework for a partnership between the Office of Regulatory Affairs (ORA) and CBER called **Team Biologics**. This partnership will use the diverse skills and knowledge of both ORA and CBER staffs to focus resources on inspectional and compliance issues in the biologics area. Team Biologics will bring FDA's regulatory approach for the biologics industry in line with other FDA Centers. The goal

of Team Biologics will ensure the quality and safety of biologic products and quickly resolve inconsistencies and bring products into compliance.

Oversight reviews have identified the following goals for more effective and efficient regulation of biological products:

- Assure a comprehensive regulatory posture among all product lines.
- Promote uniformity between CBER and the field and among FDA field components associated with inspections, policy implementation, and current good manufacturing practice (cGMP) interpretation.
- Develop and maintain a highly trained and professional work force.
- Design an organized approach to inspections with clearly defined ORA and CBER roles.
- Design a rapid and effective process for resolving ORA/CBER differences.
- Focus on an operational and policy approach that fits within FDA's existing structures and systems.
- Provide for oversight and assurances of consistent quality of work products, decisions, and actions.
- Bring about maximum efficiency of operations.
- Evaluate new methods of implementing the biologics inspection and enforcement programs.

II. Overall Description of the Approach

Inconsistency, one area of particular concern, has been noted between Centers, Centers and ORA, investigator to investigator, and between ORA

districts. Several aspects of Team Biologics will address this important area.

The transfer of lead responsibility for biologics biennial inspectional programs to ORA will result in a single FDA unit using a similar approach with all cGMP inspections. This transfer can significantly reduce opportunities for inconsistent actions and misinterpretations between CBER and ORA.

In view of the demand for technical knowledge and expertise in certain program areas, ORA will develop a more specialized and technically prepared work force. To address concerns about a lack of uniformity among FDA's blood product inspection workforce, ORA will establish a cadre of specialized investigators whose principle focus will be biologics product inspections.

The first phase of Team Biologics will focus on industries involved with blood, blood components, and fractionated products. To inspect biological products and establishments associated with their processing, ORA and CBER will develop a cadre of specially trained and certified investigators called the **Core Team**. The actual training regimen will vary with the product area, but the overall approach will be similar to that currently being implemented for medical device inspections. As additional product lines are transferred to ORA,each Core Team member from ORA will have at least a primary and a secondary specialty within the general field of biologic products.

Biological inspections will be conducted using the current ORA team inspectional approach. The assigned lead investigator or team leader will assemble an inspection team with the skills and disciplines necessary to evaluate effectively a firm's compliance status. In addition, the lead investigator is responsible for determining the timing of the inspection, the development of the FDA 483, and the preparation of the inspection report.

Core Teams will include CBER staff in biologics inspections. CBER will develop a cadre of CBER staff whose training will include technical areas, but also a comprehensive understanding of ORA's inspectional approach. This training would include courses as FDA/PHS Law, evidence development, cGMP inspectional techniques, and investigative interviewing techniques. In

Team Biologics(continued)

addition, CBER staff with product expertise will receive additional training as "product specialists" to serve as experts during the inspection process. Training of these experts will not be as extensive as that provided to the Core Team, but will include all of the courses provided to the Core Team and will be held jointly with the other members of **Team Biologics**.

Typically, all inspections will NOT be pre-announced to the establishment. However, the ORA team leader will schedule and provide advanced notice conforming to FDA activities in similar commodities.

The focus of Team Biologics -- enhanced uniformity and depth of coverage -- will result in added costs. The continuing cost of maintaining the level of expertise will require ORA/CBER to sponsor periodic training, to promote attendance at professional meetings and workshops of professional organizations and trade associations, to support periodic details to CBER, and to coordinate joint inspections to work with product experts. Another significant cost is travel since biologics establishments are dispersed across the U.S. and in several foreign countries.

Another important element of Team Biologics involves a directed focus on compliance activities. This different approach involves organizing a specialized cadre of investigators and product specialists within ORA and CBER who will serve as a resource for the inspectional teams by giving guidance on CBER related legal issues and by preparing legal actions. After the Core Team identifies compliance problems, designated ORA and CBER compliance officers will interact with the Core Team, provide support and counsel on evidence development, and draft any required administrative or regulatory action documents.

An ORA compliance officer team member will immediately contact the CBER Office of Compliance team member for CBER support of administrative, civil and/or criminal action. This Core Team is charged with jointly developing and recommending a course of action designed to resolve compliance issues. This streamlined approach to inspections allows for significant direct reference authorities to be developed and delegated by the Compliance Policy Guide as

is done with other regulated products. The Core Team will forward warning letters and more routine actions to the CBER Office of Compliance for expedited review and consistency. The Core Team will refer more complex and/or serious regulatory actions to the Office of Enforcement/ORA for handling by the *ad hoc* process, where an enforcement strategy will be developed by key Agency staff, including the Team. When possible, the Team will make the request prior to completion of the inspection. Through the *ad hoc* process, an enforcement strategy will be developed and provided to the Team for implementation.

The team approach will require the establishment and maintenance of two oversight work groups -- a Steering Committee and an Operations Group -- each with a membership tailored to their tasks.

A **Steering Committee** will be responsible for setting overall objectives and strategies, policies relating to biologics inspections, timing of the inspectional responsibility transfer, establishing quality oversight procedures, and implementing and following-up on Team Biologics.

The makeup of the Steering Committee should include senior level FDA managers to provide visibility within and outside of FDA. The Steering Committee will emphasize FDA's commitment to assure that biological products, including products derived through biotechnology, are safe and effective for their intended uses.

The role of the second work group, the **Operations Group,** is to work with CBER and ORA during the implementation phase of Team Biologics. The Operations Group will oversee the selection of the Core Team and will consult with appropriate CBER and ORA staff in the design and delivery of the training. A prime objective of the Operations Group is to establish procedures that will allow Team Biologics to establish policy. As experience is gained, the Steering Committee and management will decide if the jurisdiction of the Operations Group should be expanded to other product lines or if separate operations groups should be formed.

Team Biologics(continued)

The makeup of the Operations Group should include mid-managers and others with the knowledge, ability, and authority to make decisions and take action. When necessary, the Steering Committee, CBER, and ORA management can give the Operations Group and the Core Teams authority to act.

Resolving disputes between Core Team members is an important facet of Team Biologics. While differing viewpoints and ideas are encouraged, disagreements must be resolved quickly. The mechanism designed to resolve disputes must allow the parties to express their views informally and with as little memorandum preparation as possible. The Director of ORA's Office of Enforcement will serve as mediator and arbitrator in compliance and enforcement issues. However, on questions of health significance, the Associate Commissioner for Operations will be consulted and can convene an *ad hoc* group of suitable experts from the Office of the Commissioner or experts from FDA Centers to reach a resolution.

The changes outlined in this plan should result in enhanced efficiency of field inspections as well as the resolution of compliance issues. By avoiding duplication of effort and emphasizing the areas of expertise, ORA and CBER can excel in their individual areas of expertise which results in more effective inspections.

The inspection of blood and plasma collection facilities have a modified and less formal approach. Because of ORA’s 15 years of experience conducting blood inspections, there already exist a number of well trained blood bank/plasma investigators. However, limited updated training and the use of inexperienced investigators have caused problems with consistency and quality.

To address these problems, ORA districts will designate a cadre of appropriately trained investigators to conduct blood bank/plasma inspections. This cadre will reduce the number of investigators from 200 to approximately 125. The size of the cadre will be assigned by ORA and will be proportionate to the inventory of blood bank/plasma firms.

The entire ORA blood bank/plasma center inspection cadre will attend a one-week update training course -- the first session will be held during the fourth quarter of FY 97. Three or more training courses will be held during the first half of FY 98 depending on the number of investigators to be trained.

CBER and ORA staff should be alert for issues that would be appropriate for a one- to two-hour PictureTel training session. This training session also will serve to keep ORA investigators up to date on changing technologies and policies.

Just as FDA requires regulated industry to have quality oversight of their operations, FDA should do the same. ORA soon will implement a focused and interactive quality systems approach that will be integrated into Team Biologics. In the interim, the Operations Group will be responsible for establishing a day-to-day quality assurance program.

An essential key to the success of Team Biologics is to conduct all training jointly. This training interaction coupled with the coordination during inspections and other program activities will develop strong working relationships between the members of these mutually important FDA entities.

III. Implementation Procedures

FDA's new approach to the inspection of biologics was developed to enhance the coverage of its products. Under the direction of the Steering Committee, the plan will first be applied to the plasma fractionator industry in the fourth quarter of FY 97. After an evaluation, the plan will be extended to other biological product areas beginning the first quarter of FY 98 by issuing compliance programs and policy guides and training of additional ORA and CBER staff. As the transition occurs, all inspections will be conducted by ORA/CBER teams. The transfer of lead responsibility will be accomplished according to the following schedule:

Licensed in-vitro diagnostics -- April 1, 1998

Team Biologics(continued)

Biotechnology (IE., monoclonal antibodies and recombinant DNA-derived proteins) and allergenic products -- October 1, 1998
Vaccines and all other products -- October 1, 1999

The **Team Biologics** approach involves the following primary elements, designed to address the issues identified above:

[1] A **Core Team** consisting of certified ORA investigators, CBER certified inspectors and specially trained compliance officers representing both ORA and CBER will be used to implement this inspectional plan. Specially trained compliance staff will provide guidance and support when significant compliance issues require administrative, civil, and/or criminal actions to ensure public safety. Additional CBER staff with product knowledge will receive less extensive training to permit them to be product specialists, which will allow them to provide additional expertise during inspections.

- Team members will be selected by their respective organizations in consultation with the Operations Group.

- Core Team members should possess knowledge, skills, and abilities at a higher level than journeyman positions (field consumer safety officers need more than 30 credits, advanced degrees, and/or specialized experience/training).

- The basic certification training program for all Core Team members will consist of an intense program provided by ORA and CBER. The training program includes such topics as basic FDA/PHS Law, evidence development, cGMP inspectional techniques, investigative interviewing techniques, and appropriate specialized training (e.g. a sterilization course for plasma fractionators). CBER and ORA will coordinate details as well as attendance at professional meetings and workshops of professional organizations and trade associations.

Team Biologics(continued)

- CBER product specialists will receive additional training to provide support to the Core Team. This training will be incorporated into the training curriculum for ORA and CBER team members and the training will be held jointly.

- The Core Team would be recertified on a three-year cycle. To maintain certification status, continuous training would include annual refresher courses. Core Team members would be required to conduct a minimum number of related inspections during each year and maintain continued interaction with professional organizations and associations. During the certification cycle, ORA members will serve at least one detail in CBER, and CBER team members will serve at least one detail to the field.

- An ORA team member will generally serve in the lead role for all inspections.

- The ORA lead investigator will determine the makeup of the inspection team and the length of participation in accordance with general procedures developed by the Operations Group.

- To be most effective, ORA members will be trained in more than one specialty area, as appropriate.

- Team members (Compliance officers from ORA and CBER) will play an integral role in the development of legal actions. They will become involved when potential compliance issues are identified and prepare enforcement actions as the inspection progresses.

- FDA 483s and establishment inspection reports will be prepared and submitted jointly for legal/administrative actions by the Core Team in a timely manner and in accordance with procedures in the RPM and other guidance materials.

- ORA members will be assigned to and supported by their

particular district offices. While they could perform other inspections on behalf of the district, their first priority will be the biologics inspections.

- Funding would be provided by both CBER and ORA.

This plan initially will be applied to the plasma fractionator industry with the selection of a small group. The recommended makeup is 5-10 ORA investigators, 2-3 CBER inspectors, and 2 compliance officers from each organization. Three to five product specialists from CBER would also be trained at a less intensive level. This group would be provided training specific to plasma fractionated products and related inspectional procedures.

[2] A **Steering Committee** will be responsible for overall biologics policy as it relates to the inspectional activities and quality assurance oversight, including:

- Facilitating the transfer of inspectional responsibility and related implementation activities from CBER to ORA.

- Procuring resources.

- Analyzing the Core Team's work to determine if consistency is being achieved and if the rate on primary compliance issues is being reduced.

- Facilitating the development of compliance programs, compliance policy guides, and training to implement this new approach to other biologic products.

- Developing enhancements to this approach to be tried by the Operations Group to facilitate implementation to other product classes.

- Expanding the Operations Group to additional product lines or establishment of additional groups for those products.

- Evaluating this inspectional approach 1 year after implementation.

The Steering Committee will be comprised of the following (or their designees):

Office of Commissioner:

Deputy Commissioner for Operations
Deputy Commissioner/Senior Advisor to the Commissioner
Chief Counsel

ORA:

Associate Commissioner for Regulatory Affairs
Director, Office of Enforcement
Director, Office of Regional Operations
Chair, Biologics Field Advisory Committee
RFDD member, Field Advisory Committee

CBER:

Director
Deputy Directors
Director, Office of Blood
Director, Office of Compliance

[3] An **Operations Group** will be responsible for actual implementation and day-to-day oversight, including:

- Preparing guidance documents needed to establish the Core Team.

- Preparing inspectional guidance documents as needed for

Team Biologics(continued)

inspectional activities.

- Planning the direction the inspectional program will take as dictated by technology, regulations, etc.
- Establishing an overall inspectional plan/schedule.
- Recommending the development of additional policy, regulations, or enforcement strategies based on inspection and enforcement experience.
- Serving as a resource for the ORA field offices for resolution of policy questions related to blood/plasma inspections.
- Evaluating the composition of the Core Team to determine if additional/different members are needed.
- Establishing *ad hoc* task groups to accomplish specific tasks. Each such task group will have an operations group member.

The Operations Group will be comprised of the following (or their designees):

ORA:

Director, Office of Regional Operations
Director, Office of Enforcement
Chair, Biologics Field Advisory Committee
DEIO representative
OE representative
National Expert

CBER:

Deputy Director

Associate Director for Policy
Director, Office of Compliance
Director, Office of Blood
Director, Division of Hematology
Director, Division of Case Management

IV. Dispute Resolution Procedures

The success of Team Biologics will depend on the prompt resolution of disagreements between the members of the inspection team and between ORA and CBER. To this end, a dispute resolution process will resolve disagreements regarding inspectional and regulatory issues. The Director of ORA's Office of Enforcement will work with Team Biologics to resolve the dispute or promptly convene an *ad hoc* of ORA/CBER staff to reach a resolution.

Where the dispute relates to a potential health hazard, the Associate Commissioner for Operations will be consulted and can convene an *ad hoc* group of suitable experts from the Office of Commissioner or experts from the Centers to reach a resolution.

V. Pre-License Inspections

In order to more closely follow the plan used in other Centers, the Operations Group will review the feasibility of ORA taking the lead role as it relates to product manufacturing/GMPs for pre-license inspections. This review will include field tests to determine the impact on Prescription Drug User Fee Act time frames. Final approval authority for license applications rests with CBER. ORA/CBER inspection team makeup will follow the Core Team plan described above, including the use of appropriate product specialists.

VI. Blood Bank and Plasma Inspections

Team Biologics(continued)

This inspectional approach of blood banks and plasma inspections will be implemented at the beginning of FY 98 with the establishment of a certified blood bank/plasma investigator program. The number of investigators conducting these inspections will be established by ORA and have a direct relationship to the inspectional workload. This will allow ORA to focus a specially trained cadre of field investigators on the activities under this high priority program which in turn will address a number of the concerns raised in the recent GAO Report.

CBER and ORA will develop additional training and guidance materials, and the Operations Group will provide an additional resource to both CBER and ORA field offices by providing a focal point for resolution of policy or a forum for discussion of regulatory issues.

Director, Center for Biologics Evaluation and Research	Associate Commissioner for Regulatory Affairs