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# Team Biologics Inspection and cGMP Compliance of an Allergenic Extract Manufacturer

Team Biologics was organized to try and bring uniformity to the inspection of the biologics industry, and to ensure that the GMPs were enforced in a manner consistent with the field inspections.

by  
**Mike Durschlag**  
Director of  
Laboratory Operations  
Allermed Laboratories, Inc.

**A**llergenic extracts are a branch of biologics under the jurisdiction of the Center for Biologics Evaluation and Research (CBER) Division of Bacterial, Parasitic, and Allergenic Products in the Office of Vaccines Research and Review. Industry's compliance with current Good Manufacturing Practice (cGMP) is monitored by the Team Biologics Core Team.

Team Biologics consists of the "Blood Bank Cadre" and the "Core Team." The periodic cGMP inspections and compliance operations of plasma-fractionated products, biotechnology-derived therapeutics, allergenics, vaccines, and In Vitro Diagnostics (IVDs) are now led by investigators and compliance officers in the core team. The investigators in the blood bank cadre perform inspections of blood banks, plasmapheresis centers, and tissue banks. The cadre members report to their Office of Regulatory Affairs (ORA) district. The core team investigators report to the Office of Regional Operations (ORO) headquarters; core team compliance officers report to the Office of Enforcement (OE).<sup>1</sup>

Team Biologics was organized to try and bring uniformity to the inspection of the biologics

industry, and to ensure that the GMPs were enforced in a manner consistent with the field inspections.<sup>2</sup> Prior to the formation of Team Biologics, biologic manufacturers were inspected biannually by CBER laboratory personnel. There has been a transition period, during which the older biologic manufacturers experienced a change in inspection emphasis. The transition has involved joint inspections by core team members and field personnel, using the same core team members to inspect different companies within the same industry. It also includes nationwide weekly teleconferences of Team Biologics' Consumer Safety Officers (CSOs).

From one viewpoint, these changes in the inspection process have resulted in more consistent expectations and enforcement. Other improvements in the actual inspection have included application of scientific rationale to issues specific to one industry, published inspectional guidelines<sup>3</sup> that provide a company with Industry-specific guidance, and annotated 483s. If two consecutive annual inspections are conducted and Voluntary Action Indicated (VAI), the company may be placed on a

two-year cycle with pre-announced inspections.

As in the drug industry, there are other enforceable regulations outside of 21 CFR 211. In addition to applicable regulations under Subchapter C, Part 200, biologics are also regulated under 21 CFR Subchapter F, Part 600. Allergenic products are required to comply with the additional regulations listed in 21 CFR 680.

There are eight federally licensed allergenic extract manufacturers in the United States. These companies are generally small in comparison to drug manufacturing establishments, employing from 20 to 300 people. Since this industry is small, most extract manufacturers have fewer internal resources available to them in comparison to the larger companies. Yet, there is still the need to meet the same requirements as larger drug or biologic companies and manufacture quality products. Therefore, there is a significantly larger percentage of resources that extract manufacturers must invest in compliance than in comparison to larger companies.

This article looks at one company's approach to compliance within the allergenic extract industry, and how they have interfaced with Team Biologics personnel. This article will conclude by summarizing what is believed to be successful and unsuccessful policies designed to produce a successful inspection.

This particular firm has had two inspections since Team Biologics began inspections of allergenic extract manufacturers. The following comments relate to the firm's actions in preparing for a Team Biologics inspection, beginning in late summer of 1998.

### **Pre-Inspectional Activities**

The company knew that the first Team Biologics inspection would occur sometime after October 1, 1998.<sup>4</sup> The approach to the impending initial Team Biologics inspection was two-fold. First, it was important to listen to the experiences of other companies that had been inspected. To accomplish this, company personnel attended industry meetings in which representatives from the IVD industry discussed their experiences with Team Biologics.

Although many companies hesitate to discuss specific results when they are considered Official Action Indicated (OAI), documents listing the CSO's observations became available and were published in industry trade journals and newsletters. There were indications that many companies

were the recipients of regulatory action in the form of Warning Letters and Consent Decrees. Warning Letters were just starting to become available on the Internet about this time.

Prior to October 1998 and the implementation of Team Biologics inspections, almost all allergenic extract manufacturers had received a Warning Letter, as CBER began changing the way it inspected companies. After October 1998 and the implementation of Team Biologics inspections, it was clear that this trend was continuing among allergenic extract manufacturers, and companies needed to quickly learn what to do to avoid more severe consequences.

Personnel were primary resources in developing good compliance status. One thing that became clear was the importance of having knowledgeable people on staff, especially people who had worked in the drug industry and were familiar with field inspections, since the "new" biologics inspections were similar to drug inspections. The firm held meetings with personnel and reviewed lists of compliance observations, concentrating on correcting the most common issues within the operation and proceeding through the less common issues.

Another helpful reference is CPG 7345.001, "Inspections of Licensed Allergenic Products." The firm performed a comprehensive internal audit, looking at the details that were mentioned in the guide, to try and ensure it had been effective in its assessment of potential problem areas.

Company personnel reviewed their previous Establishment Inspection Report (EIR) and FD-483 to ensure they had corrected those problems. The 1998 FD-483 contained 41 observations in 18 categories. A Warning Letter based on that citation was issued. The firm did not want to repeat those results at the next inspection.

### **First Team Biologics Inspection**

In May 1999, the company was inspected by two representatives from the Team Biologics core team. One investigator had a background in biologics having worked for CBER, and the other investigator had field inspection experience in the drug industry. They announced that their intention was to perform a comprehensive cGMP inspection. They gave company personnel a target of two weeks as the length of the inspection, provided that significant and unexpected compliance violations were not uncovered during the inspection.

The approach to the inspection was to provide complete information on whatever was requested, without expanding the topic of discussion. This included showing the investigators deviations or excursions associated with the specific issue. Staff attempted to focus on current compliance issues rather than past issues, as they were not trying to enhance the number of observations received. The approach was partly successful. The company determined its success from the observations discussed below.

The CSOs had two approaches to evaluating the company's compliance status during this inspection. The first was ensuring that all the observations from the 1998 inspection were corrected according to a commitment to the Agency. To confirm this, company personnel went through each

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item, showing the investigators documented corrections. It was important to scientifically justify each item and conclusion. The second approach used was to verify, in some detail, that current systems were compliant. The inspectors took nothing for granted and performed a thorough inspection. Most of the issues that were reviewed came directly from the "Inspections of Licensed Allergenic Products" Guidance (1998). Within the compliance inspection, the investigators concentrated on internal investigations including sterility, environmental monitoring, and laboratory Out-of-Specifications (OOS). Since allergenic extracts are sterile injectables, aseptic practices are critical. Sterility assurance was a key indicator of the level of control associated with the company's manufacturing operations, and therefore was examined in detail. Validation of aseptic filtration and filling also were important measures evaluated during this inspection.

Another level of the inspection was a focus on deviations and change control. All deviations performed since the previous inspection were reviewed. Deviations were evaluated for their potential to

affect the product. Reprocessing and rework procedures were evaluated. One accepted form of reprocessing at the time was refiltration of final product that failed sterility testing. This process was actually included in the approved licenses for the company's products. However, the investigators informed personnel that, even if the investigation of a final sterility test failure indicated that the product was within specifications after a refiltration, they would no longer allow reprocessing by refiltration of final product that failed sterility testing due to the excess manipulations that would have to be performed. This policy is now routinely enforced within biologics. Based on this philosophy, company personnel subsequently applied this rule to bulk sterility test positives. It was felt that, unless the company's staff members were 100 percent sure that a

positive sterility test was not indicative of product contamination, they would not release on retest. Retest would only be performed as part of the sterility test investigation.

Production of allergenic extracts can be divided into two categories: bulk extracts and prescription compounds. Bulk extracts are produced as "lots"

of product, similar to other biologics or drugs. Prescription compounds are manufactured in a pharmacy operation, based upon a physician's prescription. Since the final products are sold directly to physicians, many physicians opt to have the dilutions performed by the manufacturer.

In the pharmacy operation, vials are manufactured with a needle and syringe through a rubber septum or with a pipette and open vial. Each one of the prescriptions is sterility tested per 21 CFR 680.3. The operation therefore consists of thousands of sterility tests performed annually. A sterility test failure rate of greater than 0.5 percent (1 failure in 500 tests) in this type of operation would be considered suspect.<sup>5</sup>

Other investigational techniques employed were review of videotapes of the water system welds and smoke studies of filling and filtration rooms. The CSOs also reviewed data supporting the number of air changes per hour, to ensure that the facility was properly constructed and maintained.

One lesson learned was that, since investigators concentrated on internal practices dealing with investigations, deviations, and reprocessing, it was

advantageous to have a flowchart available. The flowchart made it easy to show the investigators how the company dealt with product failures, OOS, and investigations (see *Figure 1*). From the flowchart, the company progressed to the actual procedures and review of the investigation. Similar flowcharts were helpful to explain how complaints and adverse reaction reports were handled.

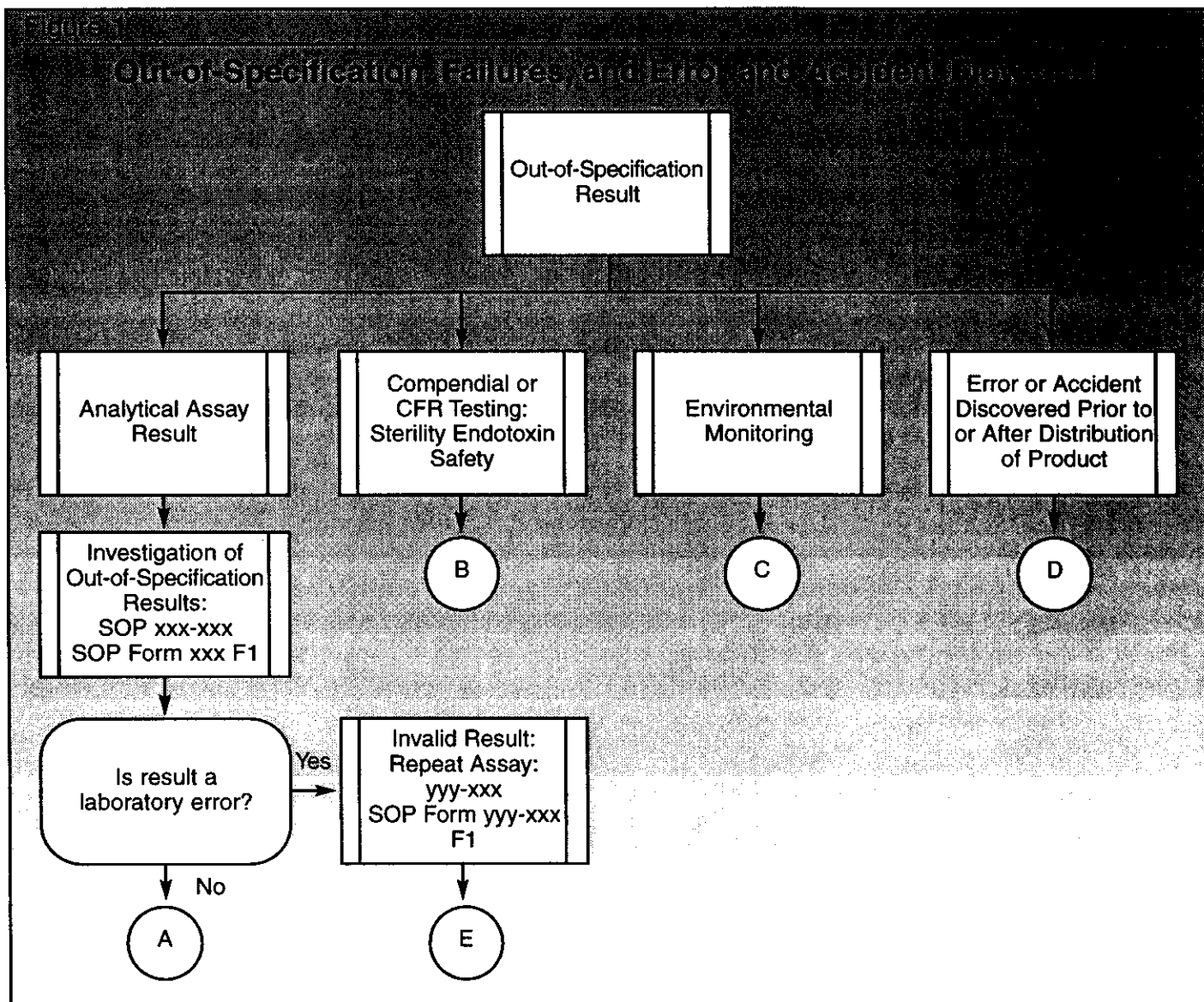
The results of the Team Biologics inspection indicated the company had progressed significantly in terms of their expectations from 1998. However, work still had to be done. The CSOs left personnel with observations concerning:

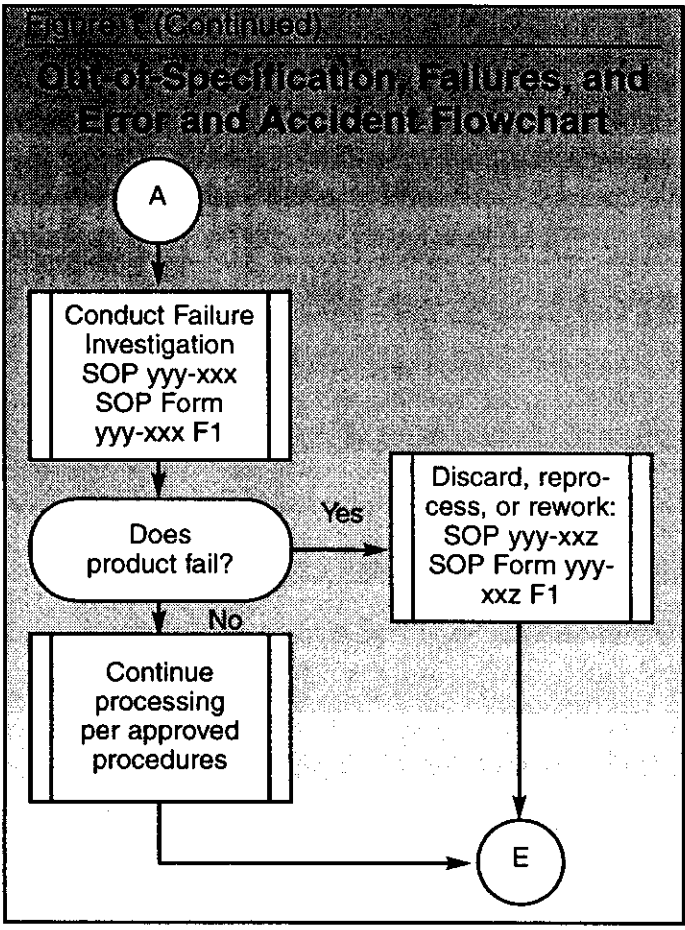
- Validations that were in-process during the inspection, but had not been completed
- Insufficient cleaning validation studies in that they did not use a large enough sample of

different types of items

- Lack of investigation into fluctuations in the number of air changes per hour
- Air velocity measurements had not been taken at the height of the work area, but had only been taken at a specified distance from the filters

Based upon the inspection, company personnel identified other areas of concern that they felt needed to be addressed. Most of the time between the 1999 and 2000 inspection was occupied with additional validation studies designed to bolster process validation. According to FDA, many older biological products have not had adequate process validation performed, and they expect every company have either retrospective or prospective validations performed on their product.<sup>6</sup> Therefore, personnel





went back to reviewing internal audits, guidances, and guidelines and attended Industry meetings.

### Two Important Issues

Two important issues to allergenic extract manufacturing were developed during this time. The first involved Bovine Spongiform Encephalopathy (BSE). This was not a new issue, but biologic manufacturers were apprehensive of the potential consequences. The disease agent was more widespread than before, and CBER sent all manufacturers a series of letters in an attempt to discern the potential of it entering the biologics product stream. All allergenic extract manufacturers received two letters in 2000. The first was dated April 19 and was addressed to all manufacturers of biological products. It required:

- Manufacturers update their records with respect to all ruminant-derived materials used in the manufacture of regulated products
- Documentation on the country of origin and all countries where the live animal source has resided for each ruminant-derived material used in the manufacture of the regulated product

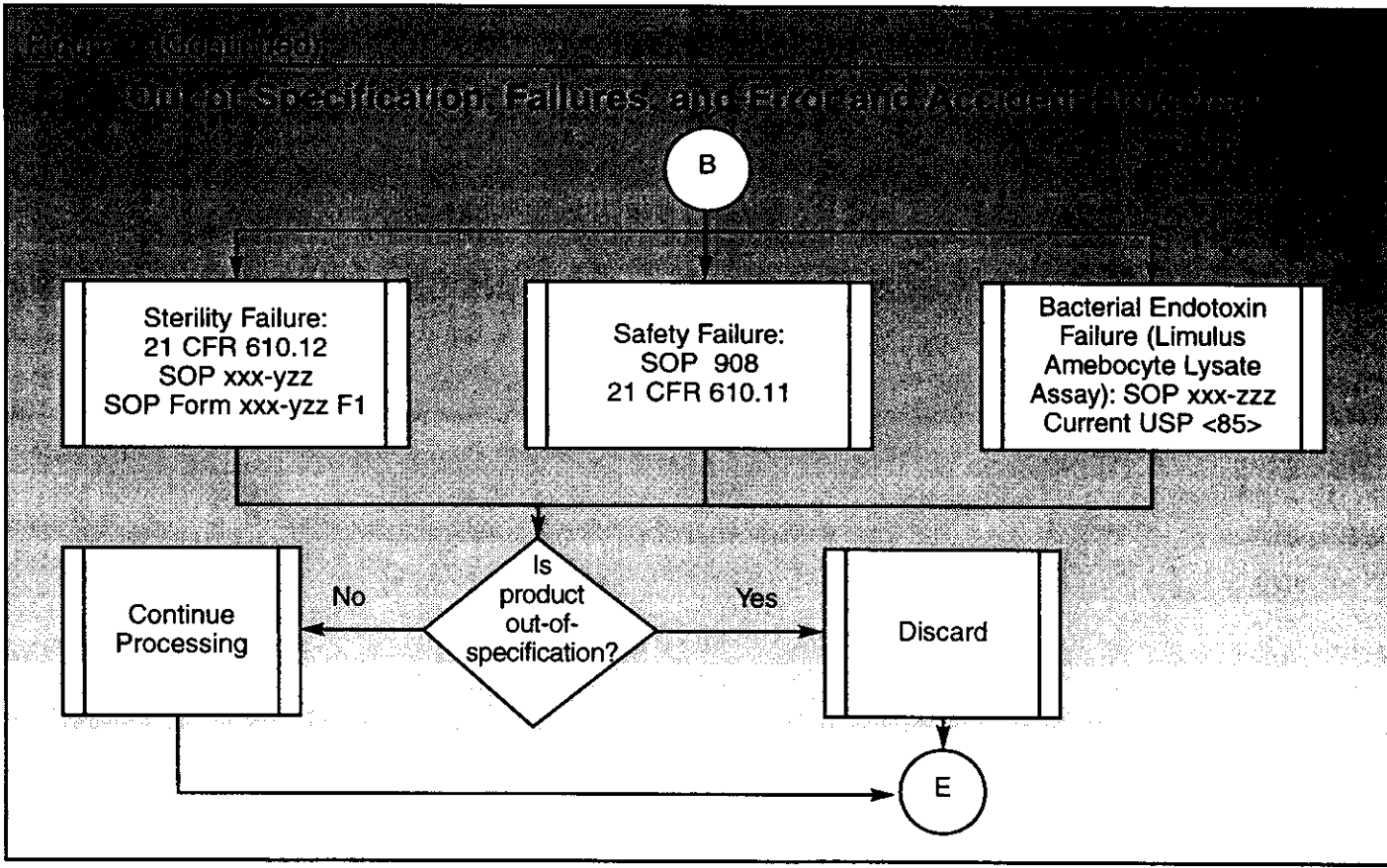


Figure 3 (Continued)

Out-of-Specification, Failures, and Error and Accident Flowchart

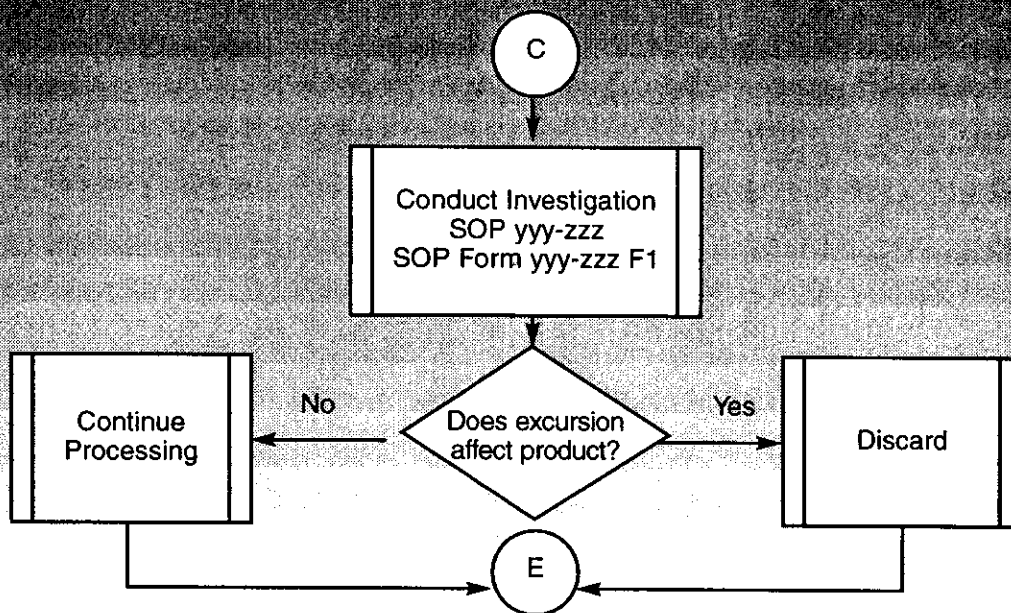
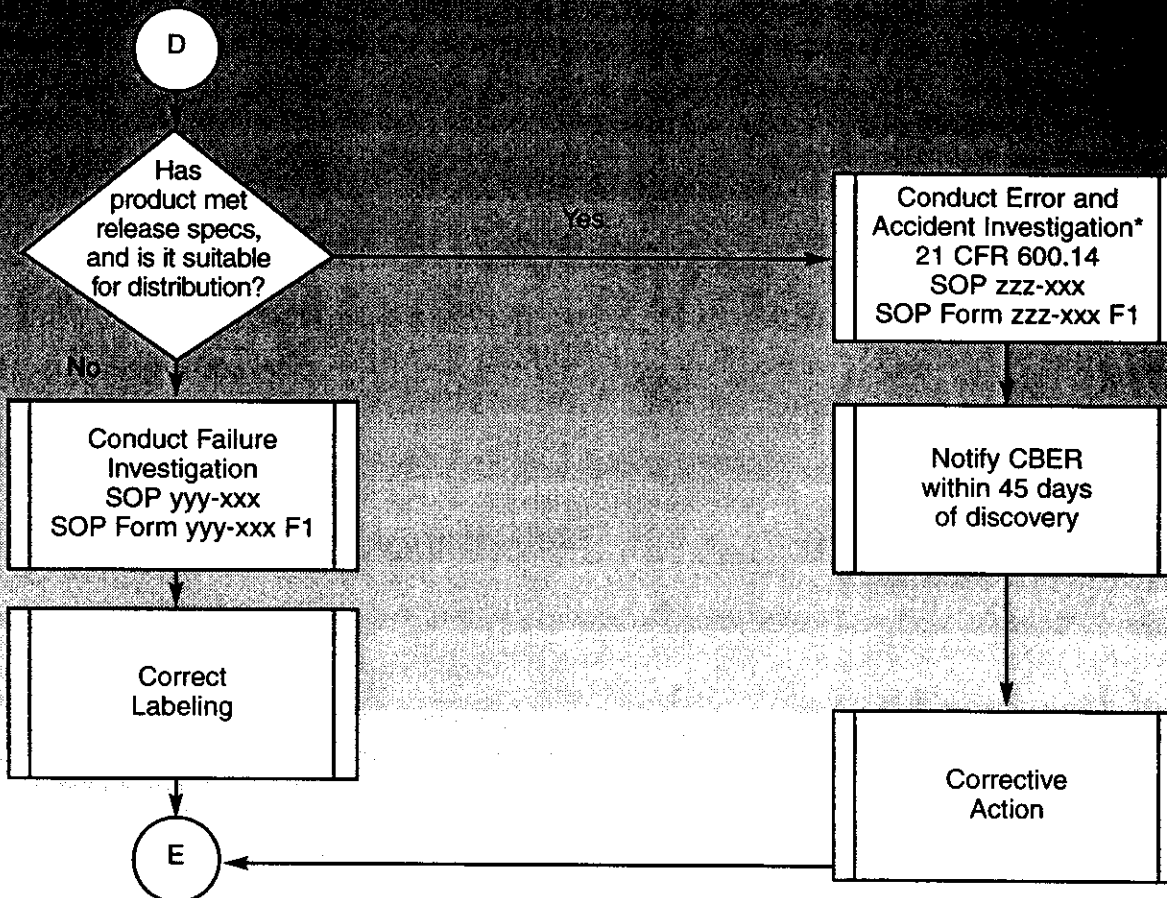
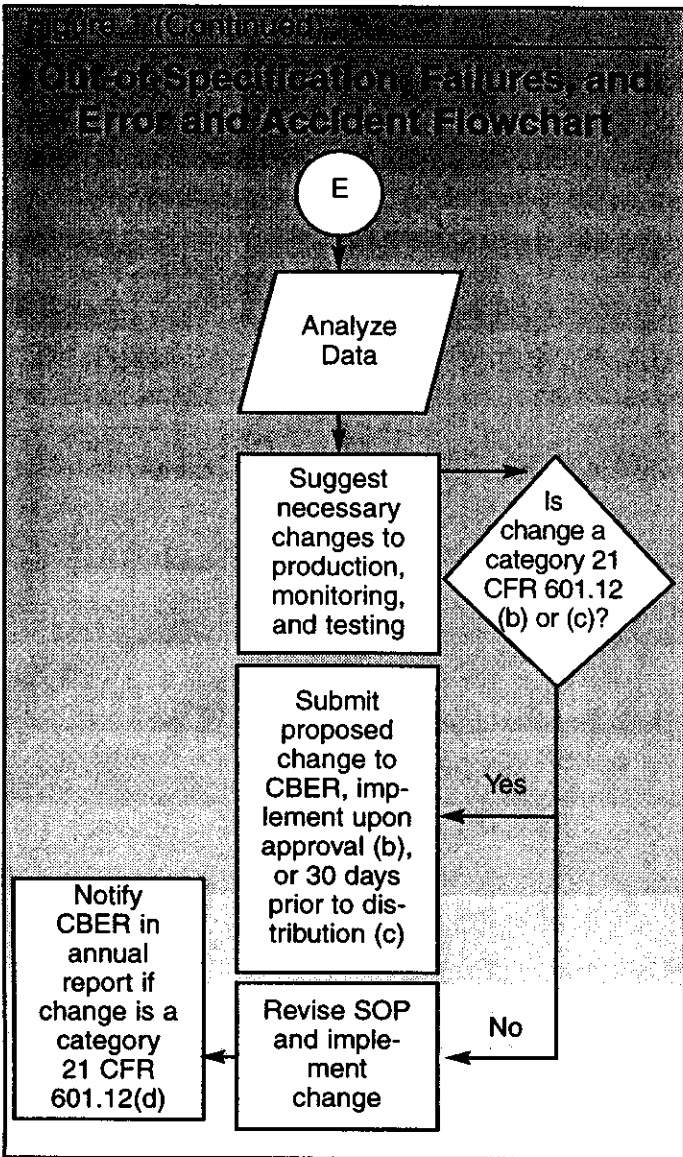


Figure 3 (Continued)

Out-of-Specification, Failures, and Error and Accident Flowchart



\* Errors and Accidents will change to biological product deviations and will differ from the example provided here.



- Maintenance of traceable records for each lot of ruminant material and each lot of FDA-regulated product manufactured using these materials
- The records be part of the product batch

The letter was followed with a fax on May 26 from CBERS's Division of Bacterial, Parasitic, and Allergenic Products regarding "specific allergenic questions." The fax contained two pages of specific questions related to materials used in the manufacture of allergenic extract. Specific emphasis was on bovine materials, but questions did extend to subjects pertaining to insect-based derivatives and molds used in production.

Based upon the responses received by CBERS in answers to these questions, another series of questions was generated by CBERS and sent to extract

manufacturers on August 22, 2000. This letter focused specifically on molds used in the production of allergenic extracts. Molds are common source materials and are usually grown on some type of agar. Certain agars contain bovine material, and CBERS was concerned with all source materials grown on these media. About 30 years prior, many of these molds had been procured from the American Type Culture Collection (ATCC) 20, and companies tried to gather information on media from the media manufacturers for lots that were used to grow their cultures. FDA is currently considering the ramifications of the use of materials that had been grown on media potentially sourced from foreign suppliers as long as 20 years ago.

The second issue of paramount importance to allergenic extract manufacturers that developed between the 1999 and 2000 inspection was a concern by the Agency for product precipitation. Allergenic extracts are manufactured from natural substances containing proteins and carbohydrates. They are extracted in an aqueous salt solution either with or without glycerin, and processed and stored at refrigerated temperatures. The filtered solution contains plant and/or animal components. These solutions may precipitate over time. Precipitation appears to be a product characteristic that is not entirely predictable and has not affected product usage by the practitioner. There have been no pharmacological differences detected between precipitated and non-precipitated products or concerns for safety. However, precipitation of products did lead to extensive inspections of manufacturer's inventories, recalls, and several 483 observations during 2000. Manufacturers were instructed to file an error and accident report with CBERS for incidents involving precipitated extract, while CBERS developed more concrete guidelines.

Company personnel believed that they needed to be proactive with respect to both of these issues. Therefore, they became committed to purchasing bovine materials from a single source so they could exert more control over processes, and limit the amount of effort expended in assuring that a specific manufacturer had not changed their sources. These internal rules affect raw materials, media for growing molds, and even sterility test media.

The company also performed a 100 percent inspection of retention samples and product inventory to check for precipitation. The policy had always been not to ship precipitated products. Personnel realized, from a review of 483s received by other

companies and through Industry meetings, that CBER had developed requirements for dealing with precipitation. CBER's position regarding precipitated products were not published, but were to be enforced through Team Biologics inspections. The following information was provided to manufacturers at a joint Allergen Products Manufacturers' Association (APMA)/CBER meeting in October 2000:

- No precipitated product can be shipped. A visual inspection of each vial must be performed prior to shipment. This was in addition to the requirements of visual inspection of each vial after manufacture.
- An error and accident report must be filed for each event.
- Manufacturers must modify their labeling to describe the actions that must be taken by the physician, in the event precipitation is discovered in the product.

At the APMA meeting with CBER, attendees were provided with a summary of Industry-wide objectionable observations by Mary Malarky, Director of the Division of Case Management. A brief synopsis of her presentation is presented:

In fiscal year 2000, Allergenic Product Manufacturers (APM) had more suspensions, letters after [Notice of Intent to Revoke] NOIR, and regulatory meetings with the Agency than in FY 1999. Outside of blood banks, APM submitted the most error and accident reports of biologic product manufacturers. In FY 2000, APM issued more recalls than in the previous three years. There were six enforcement actions taken by the Agency against APM in FY 2000. The most frequent issues leading to enforcement actions in FY 1999-2000 were: inadequate investigations and [Corrective and Preventative Action] CAPA, refiltration/reprocessing/reworking, container/closure, validation, reserve samples (Inspection), error and accident reporting, [Standard Operating Procedure] SOP deficiencies, and Annual Product Review [APR].<sup>7</sup>

The company re-examined these areas within the organization and made changes where necessary, based upon these issues. Staff performed additional analyses of precipitated products that had been identified through inspection of retention samples. They wanted to be able to explain to an

investigator why their products had precipitated. All data related to precipitation that the firm generated was placed together in study binders.

Finally, to prepare for the next Team Biologics inspection, personnel performed mock inspections and held company-wide meetings where the Team Biologics inspectional format was reviewed with employees. A book was also prepared, including information commonly requested during an FDA inspection. There are certain things that are asked for at each inspection, and personnel tried to anticipate some of those requests by assembling diagrams of the facility, Heating Ventilation and Air Conditioning (HVAC), water system, other utilities, and controlled areas showing room classifications and pressure differentials. Production flowcharts, OOS flowchart, organizational chart and deviations, investigations, and a validation list were all added.

## Second Team Biologics Inspection

In December 2000, the facility was inspected by two representatives of Team Biologics. The preparations made were very helpful. As anticipated, one of the focal points of the inspection was how the company addressed precipitated products. One of the investigators reviewed all the product retention samples and most of the product inventory for evidence of precipitation. One retention sample was found to contain a precipitate. They reviewed the shipping procedures to ensure that personnel were inspecting every product as it was being shipped. One FD-483 observation received was related to the training that shipping personnel received with respect to visual inspection for precipitation. It was "found inadequate in that no formal training to identify/recognize or quantify precipitation was conducted for the visual examination (e.g., the use of physical samples to show the type and/or degree of precipitation)." Although the company had developed standards for evaluation of precipitation as discussed earlier, it had not used them to train individuals.

Other observations made were related to microbiological validation studies that were performed, but did not contain information deemed essential by the CSOs, and SOPs that did not address specific aspects of an issue. The inspection lasted 10 days, and the company was left with an FD-483 containing 10 issues. Two were related to precipitation, one to an inadequate investigation, three pertained to incomplete microbiological validations,

one to an observation of a magnehelic gauge displaying a low pressure reading, one to inadequate indication of product status, and two to SOPs that needed to be revised. Before the investigators left, personnel had corrected seven of the 10 observations. (The investigators indicated the corrections on the annotated FD-483.)

The following tips are a summary of what was learned. Preparation before, during, and after the inspection helped this particular company prepare and deal with the Team Biologics inspections.

### **Pre-Inspection Preparation**

- ① Review professional publications (such as this one), articles, and the FDA web site for FD-483 and Warning Letter observations. Review both drugs and biologics. This is a good way to prepare individual departments for an inspection and keep them in compliance.
- ② Review the Federal Register regularly to learn about new or revised regulations. The Federal Register is the government's daily newspaper and may be found on-line at [http://www.access.gpo.gov/su\\_docs/aces/aces140.html](http://www.access.gpo.gov/su_docs/aces/aces140.html). Choose the search term "Food and Drug." Make sure to enter the "Date Range" correctly per their format. Even draft documents are valuable, since they disclose the Agency's current thinking.
- ③ Review inspection results specific to your industry. If you have contacts at other companies, they may be willing to discuss their observations.
- ④ Attend industry compliance meetings that are co-sponsored by the FDA. Most representatives are very willing to discuss specific issues you raise, both publicly and privately.
- ⑤ Be proactive. Perform mock inspections and internal audits. Institute changes that have been areas of contention at other companies. Some companies wait until they are cited before making any changes. This only leads to the inevitable FD-483 observation. The old adage is true: an ounce of prevention is worth a pound of cure.
- ⑥ Become familiar with the Code of Federal Regulations (CFR), United States Pharmacopoeia (USP), FDA guides, guidances, and inspection manuals. The advantage is knowing what you know and knowing what they will look at. Learn not only the written regulation, but understand its current interpretation. In-

terpretations change over time; expectations may be different.

- ⑦ Prepare a book(s) of information specifically for inspections. Get organized and "in control." This information should include building and utilities drawings, approach to OOS, investigations, trending, deviations, change control, recalls, adverse events, complaints, etc. Prepare other material in a state of readiness such as validations, stability data, and SOPs for review.

### **During the Inspection:**

- ① Assign an individual to take notes during the inspection. Focus on issues that appear most important to the investigators. Make two copies of all documents requested by the investigator. Provide one to the requester and keep one for reference after the inspection.
- ② Do not try to impress an investigator that you are more knowledgeable about a subject than he or she is. Show the facts and let them draw their own conclusions.
- ③ Do not argue with investigators. If there are issues that may be decided either way, they will decide against you if you constantly argue. Feel free to debate issues that you feel justified in defending. The best time for this is during the daily wrap-up session (see next point).
- ④ Ask for a daily wrap-up session to review any objectionable issues. Choose carefully any issues you feel are unjustified. Look specifically for issues you can defend with data. Ask the investigator for a reference for issues that are not clearly violations.
- ⑤ Be comfortable with your justifications for deviation, change control, and investigation corrective actions, as you may have to defend them. Make sure your validations show these issues. One investigator stated at an inspection that he had confidence in what was said and done because he saw the company had not presented "perfect" validations.
- ⑥ Correct issues immediately if possible. If you agree with the CSO's comments, write a deviation, error and accident report, OOS, change control report, or SOP revision quickly. Present the changes to the investigator. Review your document change control procedures prior to the inspection, and assure you have a system that is not cumbersome. Weigh the number of reviewers required to enact document approval

and the length of time it takes to move through the system. If you have a system that requires an unusually long review process, you won't be able to have your FD-483 annotated that an observation was "corrected" or "corrected and verified." The ability to make timely changes enforces your company's commitment to compliance.

- ⑦ Review all documents before providing them to an investigator(s). Assign an individual to review the materials that have been requested prior to delivering them to an investigator. He or she should ensure that they are the correct documents, without delaying timely delivery of the documents to the requester. It is not in the company's best interest to deliver documents that were not requested. This could be an indication that the company is not in control. It could also result in unnecessary review and a delay in the completion of the inspection.

#### Post Inspection:

- ① Write an inspection summary based on the notes that were taken during the inspection. This may be helpful when discussing specific issues, and informative to senior management.
- ② Conduct a meeting of responsible personnel after an inspection. Review the results of the inspection and each FD-483 item. Assign responsibility and set a time for addressing each FD-483 issue. Depending on the number and complexity of the FD-483 items, set a target for sending a written response to FDA. If possible, plan to send a response within two to four weeks of the conclusion of the inspection. Weigh the benefit of delaying the response to complete the work against submitting a timely response reinforcing your commitment to compliance. A quick, complete response demonstrates your commitment to correcting observations, and may be a factor in determining if you receive a follow-up Warning Letter.
- ③ Include documentation necessary to support your position in your response. This includes SOPs, validations, and license commitments. Where validations or repairs need to be performed, include a time commitment in your response. This again shows your willingness to cooperate with the Agency.
- ④ Sometimes issues are discussed between the

company representative and the CSO that may not find their way to the FD-483 because they are not clear violations of cGMP, but should be corrected. It could be a subject of future interest to investigators, or just an issue that should be corrected. In one example during an inspection, the investigator asked if the company had set a requalification time for the holding period of sterilized items. Since the initial work had recently been conducted, it was not a written observation. After the inspection, responsible individuals met and agreed it was a good idea to set a requalification period. This was implemented to prevent the same issue being raised in the future.

- ⑤ Currently, Team Biologics automatically sends each firm a copy of the EIR. Review the EIR with responsible staff and implement corrective actions where appropriate.
- ⑥ Conduct regular meetings with staff assigned to correcting the deficiencies. Make sure everyone is aware of his or her time commitments, and steady progress is made until all tasks are completed. At this stage of the process, the most critical issue is adhering to commitments. As items are completed, place a copy with the inspection documentation. Maintain all inspection documentation together for reference. This information will be valuable prior to and during the next inspection. When all items have been addressed, conduct an audit to insure proper implementation of the commitments. □

#### About the Author

*Mike Durschlag has worked in the biologics, pharmaceutical, and medical device fields for more than 20 years. His experience began in manufacturing, progressed to quality control, and later to quality assurance and compliance. Durschlag's current position is Director of Laboratory Operations at Allermid Laboratories, Inc. in San Diego, CA. Prior to Allermid, he worked for Amylin Pharmaceuticals as Senior Manager of Quality Assurance Manufacturing. He has also served as QA/Compliance Manager at Center Laboratories, a division of E. Merck. He spent some years in the generic drug industry after eight years in manufacturing and quality control of blood derivatives at the New York Blood Center. Durschlag has a bach-*

elor of science degree in Biology/Chemistry from SUNY (Buffalo/Brockport) and an MPA from Long Island University, C.W. Post. You can reach him at 858-292-1060 or by e-mail at [mdurschlag@allarmed.com](mailto:mdurschlag@allarmed.com).

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