

Root Cause Analysis for Drugmakers

From the Editors of

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& DRUG LETTER**

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Introduction

Whenever regulatory authorities anywhere in the world perform an audit of a drug manufacturer, one of their most frequent findings remains the inadequate performance of the investigation of deviations. Authorities expect stakeholders will carefully investigate deviations to identify non-compliance, intervene and then evaluate the effectiveness of that intervention. Without adequate investigation and root cause analysis (RCA), those stakeholders cannot effectively identify and design successful interventions. In fact, organizations waste millions of dollars every year on ineffective interventions.

A tool such as RCA uses a defined critical analysis approach in evaluating the reason for a deviation or nonconformance. As such, RCA represents an extremely helpful investigative tool in identifying why something continues to occur or, in the absence of any actual occurrence, why a firm might experience a series of near-misses. RCA techniques include brain storming, the “5 whys” and the “fishbone diagram.” Any and all may be used to explore and further examine the causes behind an event. Firms may then use the resulting analysis to identify areas for change, as well as any recommendations and solutions that aim to minimize the likelihood of an event repeating in the future.

While an RCA provides necessary feedback on an organization’s operational performance, it also costs it both in resources and time. For that reason, industry analysts recommend that organizations may choose to investigate only those events where they believe they have a significant amount to learn.

Some organizations go so far as to create a corrective and preventive action (CAPA) for every event, although it is not always necessary. A firm’s primary goals in investigating an incident should include both discovering its cause and ensuring it does not reoccur. It is up to the firm, on each occasion, whether to take its investigation all the way back to the root cause or to merely break the chain of events to halt the problem.

Whether or not an organization conducts a full-blown RCA, it should track all deviations as to location, type, frequency and whether they are new or repeat events. In fact, industry experts believe firms should track even those unexpected events not classified as deviations because they will yield valuable baseline information.

Regulatory authorities place a high value on RCA and CAPA. Indeed, a large number of FDA observations cite inadequate RCA, ineffective investigation and inappropriate CAPA. Thus, savvy organizations should want to improve their investigatory skills to remain in compliance.

The following management report is based in part on a recent FDAnews webinar that featured Michele Piepoli, managing director of MHP Consultants, LLC, a consulting organization with an emphasis on the pharmaceutical industry.

Determining Potential Product Impact

When a deviation occurs, whether in the pharmaceutical or any other industry, the responsible firm must undertake an investigation to determine what went wrong and what damage, if any, the product might have suffered. The investigation process should include some specific steps. These include:

- Notification of the appropriate stakeholders;
- Containment action;
- Classification of the event;
- Decision to investigate;
- Determination of the root cause or RCA; and
- Review and approval process.

The effectiveness of the CAPA taken by an organization marks another key step in the overall RCA. By monitoring the CAPA, an investigative team can determine whether it truly identified an incident's root cause and then applied the "appropriate fix." If it did not, it may find itself back at square one and at the start of a new investigation.

Immediate Action Required

One of the first things an organization should consider after an event occurs is the status of the product involved. The organization should determine whether the product remains within its control or now resides outside in the marketplace. In the latter case, would that require quarantine or recall? Once the organization does identify the product's status, it should then notify its QA team and appropriate management personnel. These steps form a direct link to the RCA; organizations should approach them in a systematic way.

An organization should take the following steps before launching an RCA. The steps will help to clarify the event. They include:

- Interview personnel involved and gather the facts (who, what, where, when and how);
- Initiate a notification that the deviation has occurred;
- Decide whether to convene the Material Review Board (MRB);
- Conduct preliminary disposition of the product;
- Determine whether medical evaluation is required, if applicable; and
- Conduct post-market surveillance.

Furthermore, if an organization conducts an investigation as the result of a complaint, it should also address any patient or consumer safety issues.

Classifying the Incident

Most organizations have clearly defined criteria for how to classify an incident and when to require an investigation. Certain scenarios may not require an investigation. The following classification levels chart can assist.

Determining Classification Levels			
Level	Product Impact	Product Status	CAPA Impact Investigation Required
Documentation Error	No	N/A	No
Minor	No	N/A	Desired
Major	Potential	Not distributed	Required
Critical	Potential	Distributed	Mandatory

Using these classification levels, the spillage of bulk tablets during loading in packaging, resulting in the loss of 10 percent of a batch, might represent a minor deviation. A major deviation might involve a corporate audit that reveals incomplete staff training for employees executing a task that did not result in release of bad product. And finally, an example of a critical deviation might be represented by multiple occurrences in which laboratory analysts improperly verified data—which the FDA discovered during an inspection.

Importance of Investigations

Why bother with a formal investigation? First, it satisfies a compliance requirement. Whether an organization adheres to the FDA, EU regulations or ISO regulations, it must undertake an investigation in the event of an unplanned deviation. An organization may define the nature of the investigation, but it must perform one as a compliance responsibility.

Secondly, organizations also have an economic responsibility to investigate. Conducting an investigation and determining the root cause of an incident can be expensive, but well worth it if it can prevent future reoccurrence of similar deviations. And consider that chronic problems can potentially hurt an organization in its market, especially if those problems result in any harm to consumers.

In short, a responsible firm must demonstrate due diligence. It must make sure it has left no rock unturned in its hunt to determine the true root cause of an incident and how it affects the product in question. It must not simply seize upon the first potential cause of a problem that is revealed and close its investigation if it hopes to retain its credibility with consumers.

Furthermore, health regulatory authorities have begun citing organizations in ever growing numbers for inadequate quality oversight. That has been the case especially in instances where an organization invalidates out-of-specification test results without quality oversight, as well as in cases where RCA and CAPA prove inadequate (see Appendix E). Thus, organizations must ensure that they apply appropriate quality oversight to all procedures. Doing so helps assure a high-quality product.

What FDA Regulations Address Root Cause Analysis Requirements?	
Drugs	Devices
<p>21 CFR 211.192 Production record review.</p> <p>All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and followup.</p>	<p>21 CFR 820.100 Corrective and preventive action.</p> <p>(a) Each manufacturer shall establish and maintain procedures for implementing corrective and preventive action. The procedures shall include requirements for:</p> <p style="text-align: center;">...</p> <p>(2) Investigating the cause of nonconformities relating to product, processes, and the quality system;</p> <p>(3) Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems;</p> <p style="text-align: center;">...</p> <p>(7) Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review.</p> <p>(b) All activities required under this section, and their results, shall be documented.</p>

The Investigation

During the investigation process of an RCA, an organization must make all decisions by using a “risk-based” approach; it must determine the probability of a negative event and its consequences. It then should consider the impact or effect. Finally, it should make its decisions based on those factors, not emotion or a desire to quickly resolve a problem. Throughout the investigation, the organization must continually ask: What are the consequences and the implications of each decision?

Consider this example of a risk-based decision: The weather forecast calls for heavy rain and high winds. The authorities issue a recommendation to leave for higher ground because of the potential for flooding. Residents must evaluate their risks and the potential impacts of the decisions they make. The potential impact or effects are:

- Loss of home (no control over it if flooding takes place);
- Loss of belongings (some control because many items can be removed); and
- Loss of life (there is control if the person leaves for higher ground).

The point here is that some things may be controlled and others may not, and risk should be assessed in determining what controls to impose.

A Structured Process

The investigation process should be structured, but done so in a simple manner. It should consist of the following steps:

- Evaluate all currently available relevant information;
- Interview appropriate people;
- Communicate with appropriate stakeholders;
- Clearly define next steps;
- Decide if a “team” is needed; and
- Determine the team’s makeup and leadership.

The organization should fully analyze the situation before moving on and examining what factors contributed to the problem. To maximize an investigation’s effectiveness, the organization should gather everyone who understands the situation, including both high-level experts and frontline staff. These individuals can help in understanding the event.

As the investigation proceeds, the investigators should avoid becoming overwhelmed. Instead, they should stick to evaluating all the relevant information and following the investigation’s structure. Investigators often find themselves pressured to rush an investigation by parties that demand answers and results. However, rushing an RCA can leave the true root cause undetermined.

Strategy Meeting

The strategy meeting forms a key part of the investigation. The lead investigator must determine whether the meeting should be formal or informal and what it should accomplish. The investigator also must decide who should participate; participants might include individuals from engineering, R&D, laboratory, production or QA. Certainly, the type of incident or deviation will help dictate attendance. As always, facilitation and focus both remain key to an effective meeting.

The meeting should serve as a way to gather information by using the quantitative RCA tool called brainstorming (described in more detail later). Specifically, the meeting should address both issues of fact (what is known) and suspicion (potential root causes), yet take care to separate fact from opinion.

During the meeting, team members must determine what additional information they require and define the investigation's next steps. The individual team members should resist the tendency to work on their own, in a "silo." Unfortunately, such a tendency does arise when people may grow defensive about their functional areas; nevertheless, an adequate investigation calls for teamwork, with input and information from all impacted areas.

Common Mistakes

The investigation process can often fall victim to a number of common mistakes. The most frequently cited of these is the tendency of investigatory teams to jump to conclusions in their haste to find the root cause of an incident. They allow the conclusion to drive the data, rather than allowing the data to drive them to the appropriate conclusion.

Another common mistake, as noted previously, is to allow individuals and departments eager for answers to rush the investigation. Other mistakes might occur when individuals unfamiliar with the investigation process find themselves uncertain about how to proceed or even what information to review. A final frequent mistake consists of ending an investigation too soon.

It's critical in an RCA to keep an open mind and focus on the facts. It may be tempting to rely on expertise and opinion. While both remain important, in the end only the facts of a given case will provide the objective evidence that leads to the successful conclusion of an investigation.

Using the Right Tools

The investigatory team also must determine the appropriate tools to employ. The type of tool depends on the specific type of approach the team intends to take. Examples include:

- Exploring and learning;
- Identifying potential causes;
- Verifying and eliminating causes;
- Analyzing a process; or
- Analyzing data.

For example, when a team explores an incident, it will learn about the process and thus should use process-related tools for that phase of its inquiry. If it looks at data, it should use data-analysis tools, such as charts and graphs. If the team's objective is to generate potential causes and then hypothesize on the root cause, it should use qualitative tools, such as brainstorming or the "5 whys." And if the team's objective is to eliminate causes while verifying the root cause, it should observe the process in action, conduct additional interviews with employees and follow the procedure through until it can eliminate each suspected cause. The next section explains these tools in much greater detail.

Root Cause Analysis

After the team takes the preliminary investigation steps, it should then begin looking for the root cause of the incident. Experience has shown RCA to be the best way to discover the underlying causes of undesirable events within an organization, through the use of a number of different tools, such as causal factor charts or fishbone diagrams, to name just two. RCA allows the opportunity to trace the progression of events that led up to the incident. In that sense, it is much like solving a crime.

Data collection lies at the core of RCA. Data can be objective or subjective. They may consist of hard information (data and facts) or soft information (opinion, no data). For the purpose of the investigation, “facts” may be defined as something that may be measured or photographed—unlike opinions or judgments. Language such as “too much,” “insufficient,” or “poor” reflects opinions.

Throughout an investigation, the team must occasionally take a step back and decide if it has enough information on hand to warrant its moving forward. As previously noted, organizations commonly yet mistakenly rush forward without really understanding what they have and what they still need. Some key points to keep in mind:

- Capture all necessary information;
- Do not yet discount any data or information; and
- Be accurate, taking care to separate fact and conjecture.

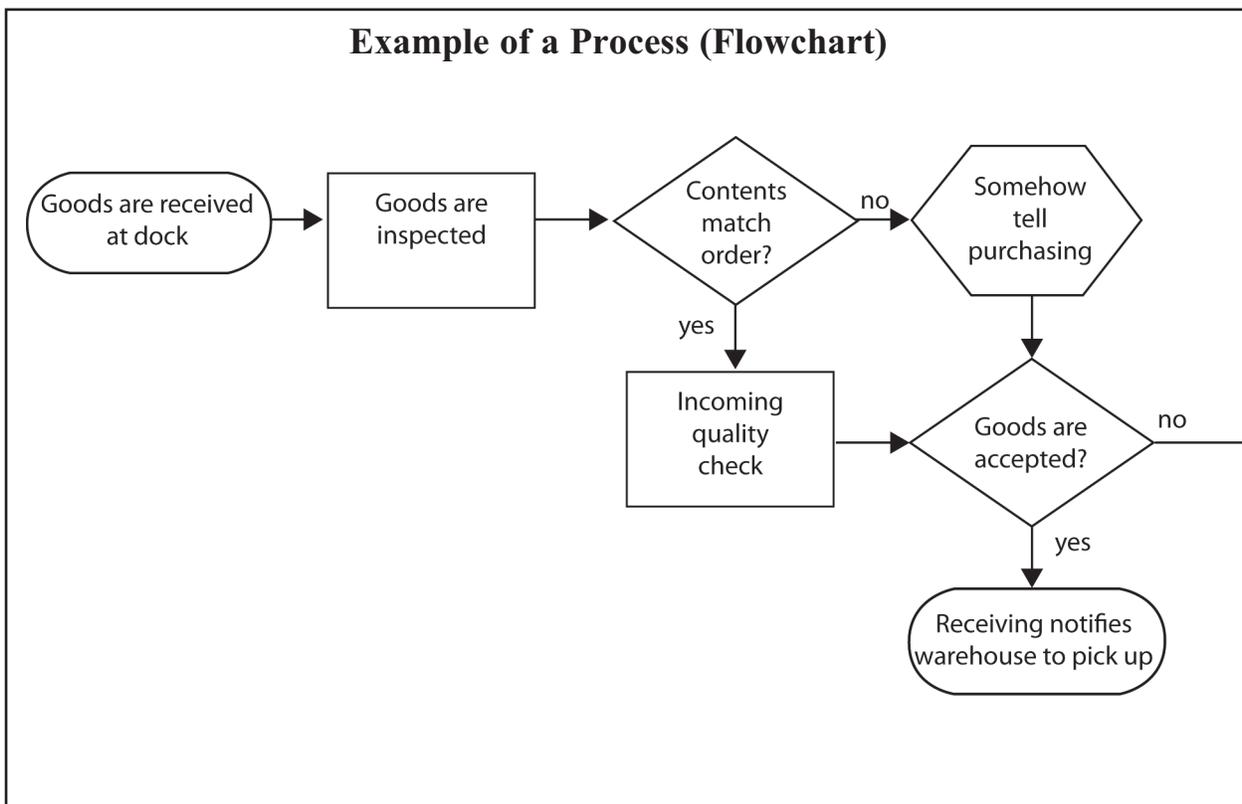
RCA Tools

An RCA can involve the use of many tools. These might include brainstorming, process mapping, cause-and-effect, the “5 whys” and more. The important thing to remember about these quantitative tools is that each is ineffective by itself, yet all are highly effective when used together.

Brainstorming remains probably one of the most popular tools in RCA. It is most effective when used early in the process. The group meets and puts all the facts on the table, saying, “this is what we know,” while continuing to look for any other potential root causes.

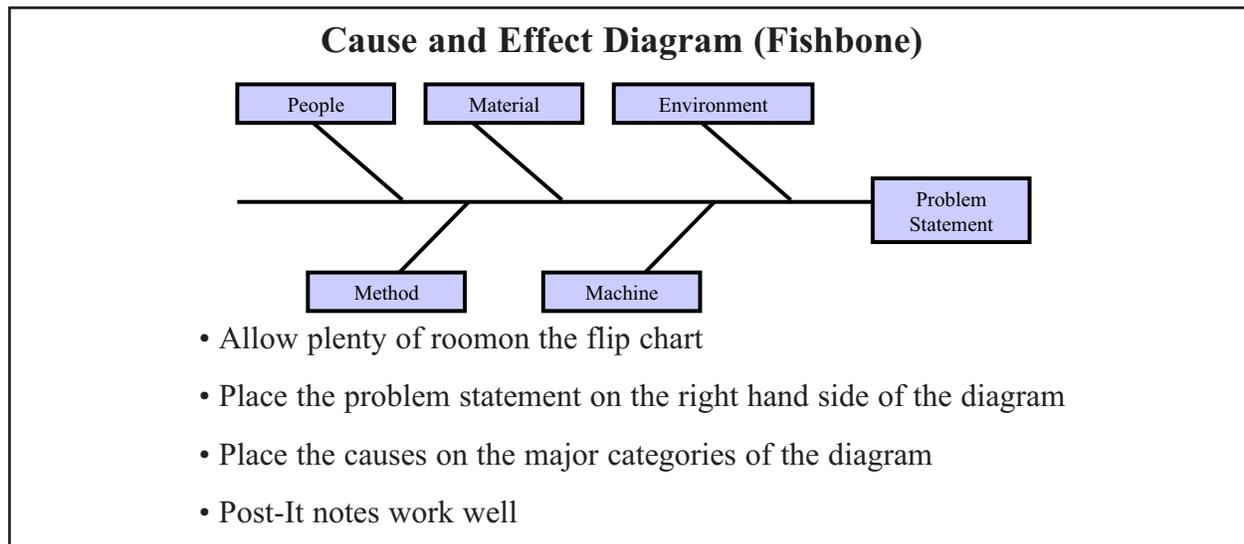
While brainstorming represents a kind of free-for-all of ideas, it can and must be done in a structured way. Don’t dismiss anyone’s ideas during brainstorming. Indeed, the goal remains to capture every possible idea, not challenge them individually. A team should refrain from making judgments during this process, given that it has not evaluated any data nor applied any problem-solving tools. After the team does gather all the necessary and pertinent information, it can then evaluate and challenge that information.

Process Mapping represents a visual representation of a process. It can be used as an analysis tool when evaluating a process to uncover a potential root cause. For example, say a problem occurs at step 32 of a manufacturing process, yet an in-process sample appeared within specifications. Then at step 62, someone identifies a problem. Thus, the investigation should focus on what happened between steps 31 and 62. Process mapping is an excellent way to break down, step-by-step, what could prove to be a contributing factor to a problem.



A process map might be compared to a recipe. Someone who bakes a cake that doesn't turn out right might look back at the recipe and try to discover where things went wrong. Perhaps the baker added only three eggs when the recipe called for four.

Cause and Effect or Fishbone Diagram includes categories that vary depending on the scenario. "People" always represent one category on the diagram along with method, machine and material. All represent potential causes of the incident.



Incident reports often cite human error as the cause of an incident, yet unfortunately it tends to be overused, according to industry experts. Instead, investigators should look beyond human error and take into account other factors. For example, employees may have received insufficient training or perhaps a batch record was not clear.

Consider the following example: During an investigation into an incident, a requirement comes to light that analysts must have their test methods out on the bench while they prepare their samples. One analyst (let's call her Mary) violated this requirement numerous times and, therefore, the team decided Mary represented the root cause of the incident. Why? Because she failed to follow proper procedure.

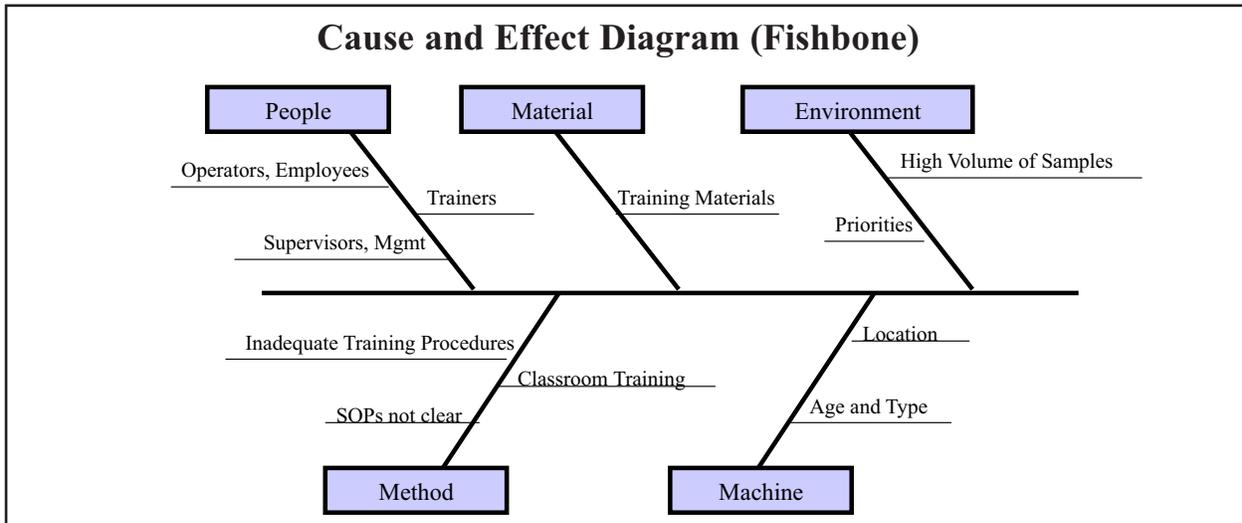
Subsequently, an investigator visited the lab and spoke with Mary. While there, the investigator noticed the very small size of her workstation and those of her colleagues. The investigator asked Mary to show her test methods, which had been sealed in binders in such a way that they could not be removed. Indeed, to prepare her samples appropriately, Mary simply could not work with her binder open on the bench. Furthermore, she had alerted her supervisor to the problem, to no avail.

Thus, Mary's failure to follow procedures was not the root cause. Instead, it lay deeper than that. First, the environment made it virtually impossible for analysts to have the test method out on the bench while performing an assay. Second, Mary had discussed the problem with her supervisor, who failed to act appropriately to solve the problem.

While this represents a very basic example, the take-away point here is to always dig deeper.

Those reviewing investigative reports must be willing to challenge conclusions just as if they had conducted the initial investigation.

The fishbone diagram forces the investigator to evaluate all categories. The diagram should be filled out as shown in the example below.



Note how the “people” rubric, operators/employees represent one subcategory while supervisors represent another. After completing the diagram, the investigative team should find itself with an outline for the investigation report it will write later.

The “5 whys” method requires the investigator to start with a precise and focused problem statement, then take the problem statement and ask “why” several times to get to the root of the problem. The chart below illustrates how it can work.

Example: The “5 Whys”	
Why?	Answer and Observation
Why was Zone A contaminated by S. aureus?	Because operator caused contamination.
Why did operator cause contamination?	Because operator was not present during training regarding plant hygiene.
Why was operator not present during training?	Because operator was on vacation.
Why was there no training follow up when he returned from vacation?	Because there is no procedure defined for follow up of missed training.
Why was there no procedure defined for follow up of missed trainings?	Because the SOP was not updated according to Quality Module.
Why was the SOP not updated according to Quality Module?	Because there is no process established for the rolling review of SOPs.

At first blush, it would appear the operator caused the contamination of Zone A after neglecting to obtain the appropriate training. On further investigation, and by asking “why” repeatedly, it appears that the organization had not put in place the appropriate procedures to ensure the operator received the proper training. The example once again points out how an investigation can jump to (incorrect) conclusions.

Interestingly, the “5 whys” approach may be combined with another tool—brainstorming—in such a way that results in out-of-the-box thinking. It also helps prevent anyone from jumping to easy conclusions. Indeed, it creates an atmosphere that forces hard questioning. Furthermore, it keeps the process moving until it starts uncovering objective evidence that will hold up to the scrutiny of regulatory authorities.

Another RCA tool is Kepner Tregoe decision-making analysis, a structured methodology developed in the 1960s for gathering, prioritizing and evaluating information. The assessment and prioritizing of risk represents an important aspect of Kepner Tregoe decision-making. For that reason, it fits well into the RCA. Here, the idea is not to find a perfect solution but rather the best possible choice, based on achieving an outcome with minimal negative consequences. It represents one way of making unbiased decisions because it limits those conscious and unconscious biases that draw attention away from the outcome.

Below is an example of a KT matrix that shows how the methodology could be used to resolve a problem.

The matrix analysis points an accusatory finger at the data restore done to the accounting department server on Friday afternoon. However, this should not mark the end of the analysis. The idea is to continue investigating and asking questions to come up with other possible causes.

Question	Is	Could be, but is not	Distinction
What is the deviation?	It is the fact that e-mail cannot be accessed.	Nothing else has been observed	n/a
Where does it happen?	It is occurring on Bill’s computer and Fred’s computer.	It is not occurring on my computer	<ul style="list-style-type: none"> • Bill and Fred are in the accounting department; I’m not. • The accounting department uses its own MS Exchange server, but I use a different email server; • Bill and Fred do not log in as super-user; I do.
When did it start?	Friday, at about 2:00 p.m.	OK before that time.	Partial restore done on accounting department server Friday between 1:45 and 2:15 p.m.

Qualitative Tools

Along with the previously mentioned quantitative tools, qualitative tools also serve a very important role in evaluating data. They include control charts, run charts, bar charts, histograms and Pareto charts. All represent excellent tools for use in evaluating trends. Say, for example, one looks at the yield on a batch, over a span of 70 batches. Is there a pattern or trend over time? Perhaps the yield did not change, but only now is starting to move to the lower range. These tools help identify any changes in the process, such as a new vendor, which could be the cause of the new pattern.

Documenting Decisions

Documenting the investigatory process represents another important part of the RCA. The process must be understandable. That way, anyone reviewing the RCA can easily identify how the root cause was determined. The task includes ensuring both due diligence and that all evidence supporting any conclusion is clearly stated. Auditors will grow frustrated if they must ask a lot of questions in order to gain a true picture of what was done.

The investigation report should document all activities, whether they are ultimately relevant or not, conducted as part of the RCA . For example, if training records prove up to date and the operator can demonstrate proficiency, the report should state that. That does not mean, however, that the report should be excessively long. The report should be complete, but strive to separate facts from either theory or opinion.

Corrective and Preventive Action

Corrective and Preventive Action (CAPA) focuses on the investigation of deviations. It does so in an attempt to either prevent their recurrence or their occurrence in the first place. To ensure the effectiveness of any corrective and preventive actions, organizations should continue monitoring them after the completion of the RCA and overall investigation.

The most common CAPA-related audit observations include “inadequate—did not sufficiently address root cause;” “inappropriate, did not address root cause;” “corrective and preventive were not clearly defined;” and “not completed in the timeline identified.” One of the biggest pitfalls associated with CAPA occurs when someone assigns corrective and preventive actions without regard for resource requirement, capacity, ownership or timeline—in other words, without a plan.

When it comes to CAPA, regulatory authorities expect organizations to ensure:

- The identified CAPA addresses the root cause;
- The solution can be implemented;
- There is clear understanding of the overall impact of the CAPA;
- Timelines and responsibilities (for implementation) have been reviewed and agreed to;
- There is a plan; and
- There is a monitoring phase.

If an organization makes it through the investigation and determines the root cause, that forms just part of the equation. In the case of an inappropriate CAPA, further problems may ensue. Thus, the appropriate CAPA should be applied and monitored to ensure its effectiveness.

FDA Observations

The below excerpt from a Warning Letter sent by the FDA to India’s Claris Lifesciences Ltd. illustrates the importance of CAPA to the agency. In the letter, the FDA cites Claris for failure to adequately perform an investigation after a deviation occurred (see Appendix E for the complete letter). Specifically, the company failed first to determine the status of its product and then failed to look for the root cause.

... Specific violations observed during the June 2010 inspection conducted at Claris India include, but are not limited, to the following:

1. Your firm has failed to thoroughly investigate the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed [21 C.F.R. § 211.192].

a. The complaint investigation discussed in the undated report submitted with Claris India’s July 2010 response to the FDA Form 483 and titled, “Complaint Investigation

Report Metronidazole Injection USP Ondansetron In 5% Dextrose Injection” (Complaint Investigation Report), is inadequate. It lacks sufficient evaluation of several complaints of intravenous (IV) bag contamination, and does not provide scientific justification and supporting evidence regarding the root cause identified. For example:

1) On April 15, 2010, your firm received a complaint from a U.S. distributor (Sagent Pharmaceuticals) informing you that Metronidazole Injection USP IV bags (lot A090744) were contaminated with a swirling mass, which the complainant identified as the fungus Cladosporium species. There is no information in the Complaint Investigation Report to show that Claris initiated an investigation to determine the root cause and extent of the problem until April 26, 2010, when Claris received this contaminated large volume parenteral and examined it.

On May 5, 2010 the same customer (Sagent Pharmaceuticals) reported that another lot of Metronidazole Injection USP bags (A090742) was contaminated with fungi (Mucor species).

The Complaint Investigation Report does not adequately address either of this complainant’s contamination findings, or the root cause of the problems. For example, your customer’s test results confirmed the presence of visual contaminants without discovering any leaks in the intravenous (IV) bags. You have claimed that the uniqueness of your firm’s method to detect leaks supersedes the customer’s methods. Accordingly, you disregarded their findings regarding the integrity of the IV bag because their test was not performed or supervised by your own laboratory. This does not address the presence of fungi. For instance, the investigation conducted by Sagent involving Metronidazole Injection USP bags (lot A090744) did not detect a leak on the IV bag tested (dye penetration by injection), even though fungi (Cladosporium species) were found inside the IV bag.

Tracking and Trending

Even after an organization concludes the investigation and CAPA processes, its work is not complete. It is important—and expected by authorities—that it will go on to track all deviations to understand their location, types, frequency and whether they represent a new problem or a recurrence of an old one. Organizations also must track those “events” not classified as deviations because doing so can provide baseline information that may help reveal a future trend.

Some organizations use the term “Level 1 investigation,” meaning it represents an “event only” and does not require further investigation. However, tracking such events allows for the collection of baseline information about ease of entries for records, forms and other documents. If an organization does not track these events, it’s impossible for it to know if it harbors a systemic or a quality system problem.

Software

Many organizations employ electronic database systems for tracking and trending purposes. Some popular systems include Trackwise (www.spartasystems.com), Microsoft Access (www.office.microsoft.com) and SAP (www.sap.com). These systems produce a variety of reports useful for management review and oversight committees as well as to monitor trends. They also prove helpful to auditors in reviewing procedures.

Key Elements of the Investigation Report

An investigation report should document all of the completed investigatory work and RCA. Writing the report comes easily if the work begins with an outline that clearly states the incident, immediate actions, correction activities, investigation activities, conclusion and CAPA. This report noted earlier how the fishbone diagram represents a good place to start an outline. Indeed, the diagram includes all of the relevant categories (people, materials, environment, etc.) that an incident might involve.

First and foremost, the investigation report must be easy to understand. It must contain sufficient information without becoming cluttered with unnecessary documentation. The reviewer should not have to ask dozens of questions in order to understand what happened in the investigation process. Finally, the report must support product disposition decisions.

When submitting comments about a report, reviewers may ask themselves some of the following questions. Reviewing them while developing the report can help anticipate questions that might come up during a review:

- Why am I requesting this change?
- Is there too much or not enough detail?
- Do I get it? Do I understand what happened, along with when, where, who, why and so on?
- Was the “immediate action” adequate?
- Are there “data” supporting the investigation’s conclusion?
- Does the CAPA make sense?

Finally, the summary represents a vital part of the investigation report and should be treated as such. Furthermore, an executive summary placed at the beginning of the report should serve to raise the reader’s interest by quickly stating the scope of the report in the form of an overview with conclusions and recommendations.

FAQ

The following question-and-answer section is based in part on a recent FDAnews webinar that featured Michele Piepoli, managing director of MHP Consultants, LLC, a consulting organization with an emphasis on the pharmaceutical industry.

Q: *Overall, what can be done to improve the quality of investigations?*

A: Taking a global approach to investigations is important to ensure consistency and alignment within an organization. Global programs are being created and structured to improve investigational skills.

Also, there is advanced training that can help one develop skills as an investigator. For example, Kepner Tregoe, as discussed earlier in this report.

Finally, some organizations have specific requirements for investigators, including certification. Of course, this usually happens in situations where they have dedicated quality personnel. In the end, this has proven to help improve quality.

Q: *Is any specific training available for investigators?*

A: Some major pharmaceutical companies are developing their own internal curricula for investigator training. However, at this time, there does not appear to be any other training available.

Q: *Auditors often comment that timelines are too long or too short or that things are being left open too long. Sometimes, the investigation is left open because the situation is being monitored. Are there any specific guidelines for this?*

A: This is probably one of the most common findings by the FDA—namely, that investigations are not completed in a timely manner. A guideline might be between 30 to 45 calendar days. If things stretch to 60 days, this would be a concern. From a lab investigation point of view, the expectation is that within three to five days, you have determined if it is a confirmed out-of-specification. At that point, if it is confirmed, it triggers a full-scale investigation.

If you are monitoring effectiveness, but the investigation is closed, the response should be, “Here is our process. Please note that the investigation was completed in the appropriate timeline, but our process requires us to do this, this and this...”

However, you can be cited if you have a 30-calendar-day requirement for an investigation to be complete and you are not completing them within that timeline or you are abusing the interim report scenario. Unfortunately, this is common in the industry because many organizations have backlogs.

Q: *Can an intermediate action prior to an investigation be considered corrective?*

A: Yes, but one must be careful about the terminology, though. So, what is the definition within an organization that has been applied for immediate action? For example, if one is in production and the one mixing vat is making a clanging noise. The immediate reaction is to shut it off or pause the process. The correction might be there could have been something wrong with an agitator.

The terms “intermediate” and “correction” are sometimes used interchangeably. It should not be an issue if you clearly define in procedures the terms “immediate action” and “corrective action.”

Q: *Does the outcome of an investigation always need to be written up as a corrective action, or can it be a corrective and preventive action or only preventive action?*

A: It depends on the philosophy of an organization. But one must also consider that, if a full investigation has been done, there should at least be a corrective action. There might not always be a preventive action, however.

Q: *Is it OK to use methods other than the causal factor or fault tree?*

A: Yes, there are a wide variety of different methods available—some from the quality arena, including the “fishbone” method. Whatever the methodology you are using, however, keep in mind that it must have some rigorous logic applied to it.

Q: *Is there any FDA guidance on this issue?*

A: There is no specific FDA guidance for performing RCAs. Typically, the regulations tend to be very broad in nature—identifying causes, identifying corrective actions, tracking corrective actions to completion. They are not too prescriptive in terms of the types of analyses that you are performing. If you are looking strictly at doing this from a regulatory standpoint, your analyses do not have to be very deep to meet regulatory requirements. What you are typically looking at is performance improvement, going beyond that to get to more detailed analyses and trying to stay out of trouble.

This is often a regulatory-driven process, but this same type of analysis certainly has benefits from a reliability standpoint—safety, security and economic reliability. So, if we can solve some of our operational performance problems, economic payback is often a key driver for most organizations when they are trying to perform these RCAs.

Conclusion

Having a deviation occur and jumping in to fix it without investigating the root cause is akin to treating the symptoms of a medical condition without trying to cure it. If someone breaks a leg, a request for painkillers may naturally follow. However, those painkillers won't heal the broken leg; nor will a "quick fix" approach resolve a deviation.

Likewise, if someone addresses only the symptoms of an adverse event, the problem itself will almost certainly reoccur (or never vanish in the first place). And at that point, of course, it will require constant fixing.

RCA represents the best "medicine" for any adverse event. It both fixes the symptoms and helps uncover the reason why the event occurred in the first place. The process helps identify the origin of a problem, using a specific set of steps and specific tools, to find the problem's primary cause.

RCA may be applied to almost any event; determining how far to go in the investigation requires some knowledge and judgment. In theory, you could keep asking "why" forever—well beyond the "5 whys." While some organizations choose to implement full-blown investigations for every event, they should understand when a significant cause has been discovered or if RCA is even required.

Conducting RCA can help to change an organization from one that just reacts to problems to a system that solves problems before they spiral out of control. More importantly, RCA can reduce the likelihood of such problems ever recurring.

Root Cause Analysis for Drugmakers

Appendices

Appendix A: An Overview of the RCA Process

Appendix B: Analysis Techniques

Appendix C: Sample Causal Factor Tree

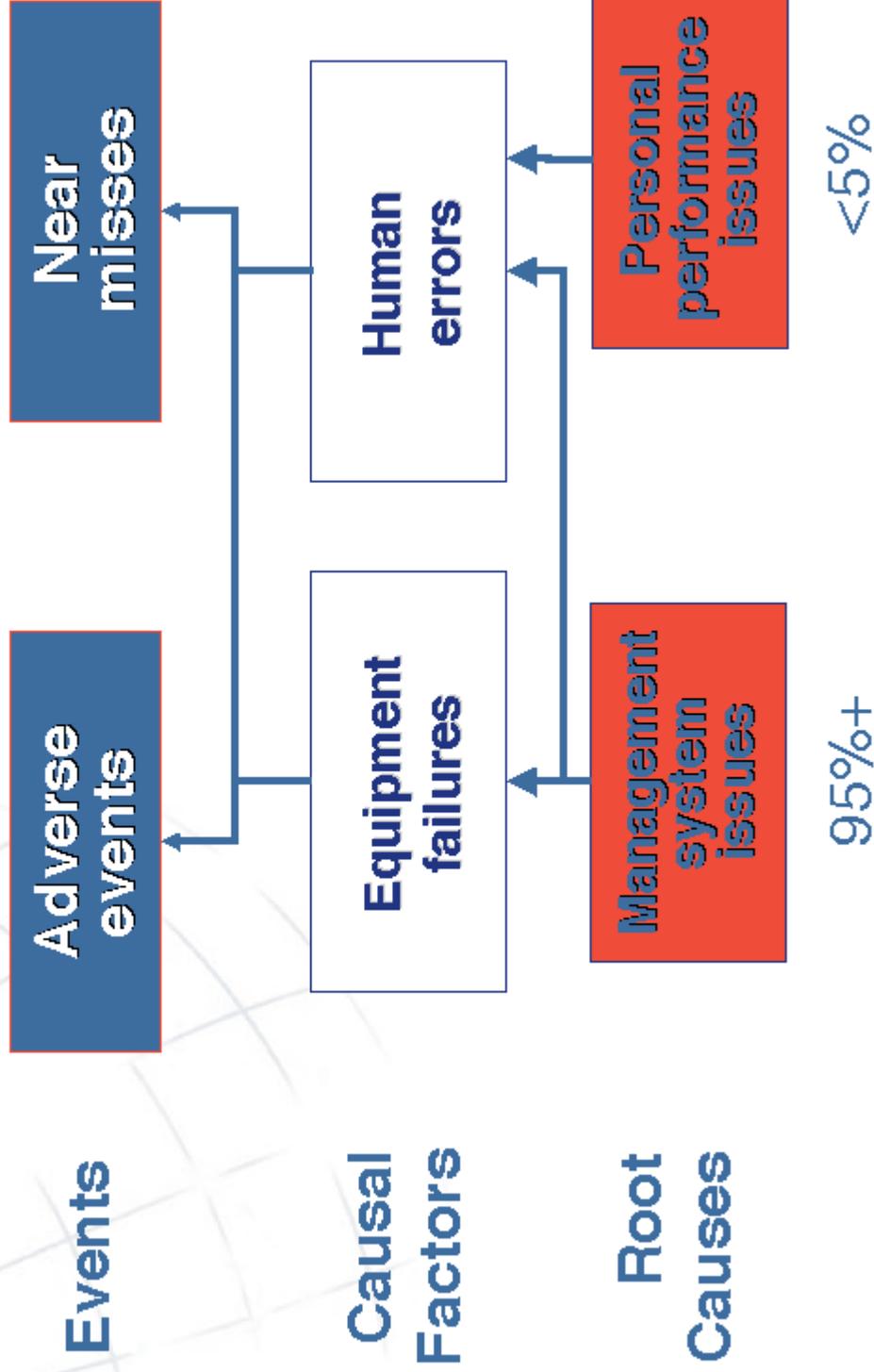
Appendix D: Example Causal Factor Chart

Appendix E: Claris Lifesciences Limited Warning Letter

Appendix A

An Overview of the RCA Process

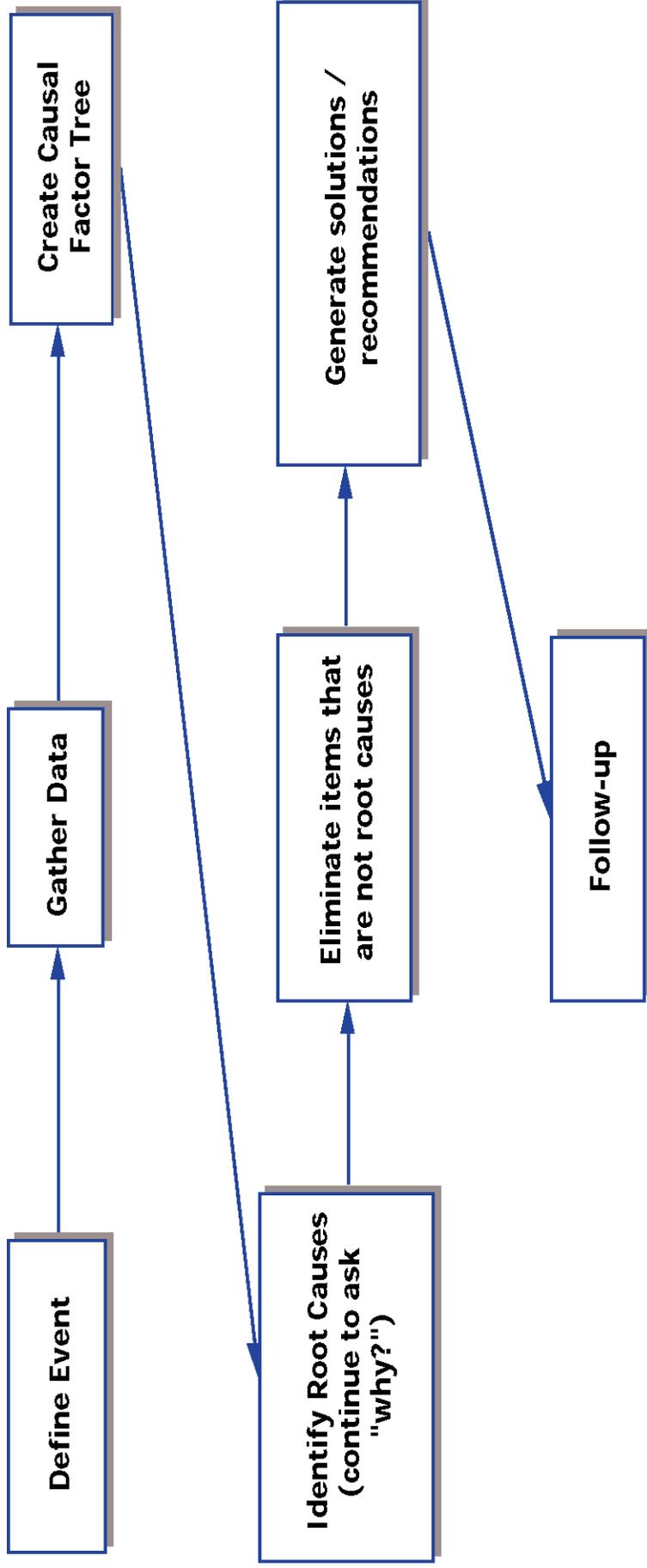
Underlying Causes of Incidents



Applicability of Analysis Techniques to Different Types of Analyses

	Causal Factor Charting	Fault Tree Analysis
Acute events	Good	Good
Chronic events (including most large, acute accidents)	Can only characterize typical event	Good
People-oriented problems (large, acute accidents)	Best	Good
Events where timing is important	Best	Not very useful
Equipment and system-oriented problems (including most chronic problems)	Good	Best

Appendix A Root Cause Analysis (RCA) Process



Appendix B

Analysis Techniques

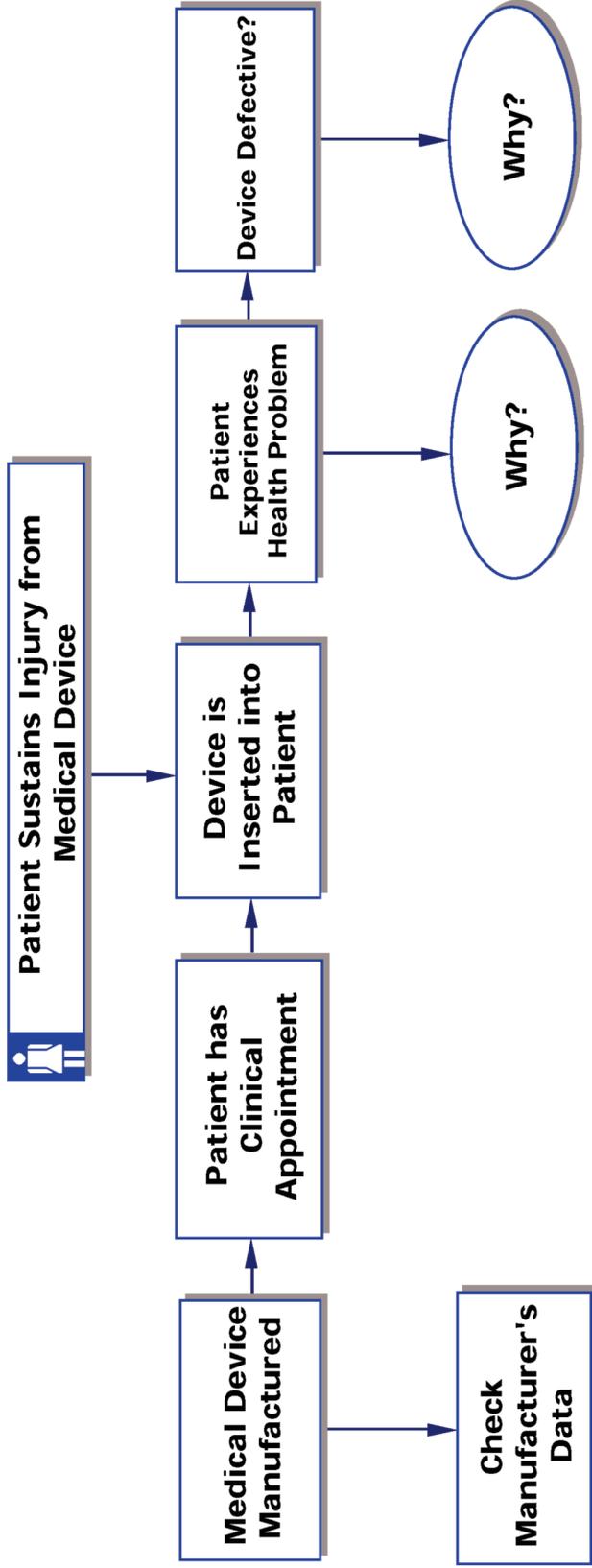
Applicability of Analysis Techniques to Different Types of Analyses

	Causal Factor Charting	Fault Tree Analysis
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Events where timing is important	Best	Not very useful
Equipment and system-oriented problems (including most chronic problems)	Good	Best

Appendix C

Sample Causal Factor Tree

Appendix C Sample Causal Factor Tree

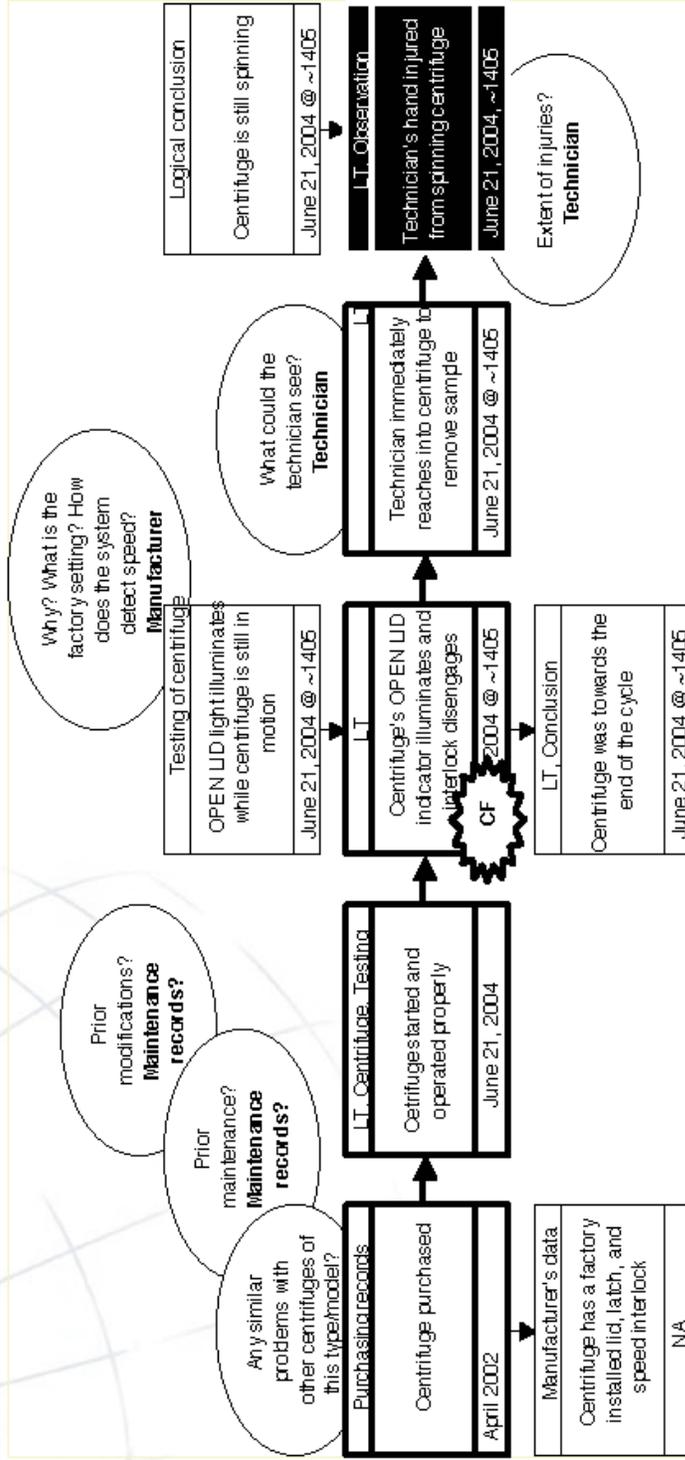


After you have identified all the possible causes, ask yourself "why?" each may have occurred. Be sure to keep your questions focused on the original issue:
Why was the condition present?
Why did the event occur?
Why did the barrier fail?

Appendix D

Example Causal Factor Chart

Example Causal Factor Chart



Appendix E

**FDA Warning Letter to Claris Lifesciences Ltd.,
Ahmedabad, Gujarat, India, dated November 1, 2010**

Claris Lifesciences Limited



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

Warning Letter

VIA UPS

WL: 320-11-003

November 1, 2010

Mr. Arjun S. Handa
Chief Executive Officer & Managing Director
Claris Lifesciences Limited
Chacharwadi - Vasana
Ahmedabad, Gujarat 382 213
India

Dear Mr. Handa,

The U.S. Food and Drug Administration (FDA or Agency), conducted inspections of Claris Lifesciences Limited, located at Chacharwadi - Vasana, Ahmedabad, India, and Claris Lifesciences, Inc. (a wholly-owned subsidiary of Claris Lifesciences Limited), located at 1445 US Route 130, North Brunswick, New Jersey 08902-3100 (hereinafter collectively referred to as "Claris"). The inspection of Claris Lifesciences Limited (hereinafter referred to as "Claris India"), took place during June 5-16, 2010 (June 2010 inspection). The inspections of Claris Lifesciences, Inc. (hereinafter referred to as "Claris U.S."), took place during July 1-13, 2009 (July 2009 inspection), and January 22 to February 2, 2010 (January/February 2010 inspection).

During our June 2010 inspection of Claris India, FDA investigators identified significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)], in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

The June 2010 inspection also revealed that Claris failed to submit NDA Field Alert Reports (FARs), to FDA in compliance with section 314.81(b)(1) of FDA's regulations [21 C.F.R. § 314.81(b)(1)(ii)], as required by section 505(k) of the Act [21 U.S.C. § 355(k)]. An applicant is required to submit, within

three working days of receipt, information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of drug product to meet the specifications established for it in the application.

In addition, based on our review of the labeling for your Sodium Bicarbonate Injection drug product, manufactured by Claris India and distributed by and through Claris U.S., and information collected during the inspections of Claris U.S. in July 2009 and January/February 2010, we conclude that Claris has marketed an unapproved new drug without an approved application. The introduction or delivery for introduction into interstate commerce of the product is a violation of sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(d) and 355(a)]. The unapproved new drug product is also misbranded under section 502(f)(1) of the Act [21 U.S.C. § 352(f)(1)], and therefore, the introduction or delivery for introduction of the drug into interstate commerce is also a violation of section 301(a) of the Act [21 U.S.C. § 331(a)].

We have reviewed responses from Claris dated August 12, 2009, October 7, 13, and 30, 2009, February 24, 2010, and July 3, 2010, but conclude that they lack sufficient corrective actions as discussed below.

CGMP VIOLATIONS

Specific violations observed during the June 2010 inspection conducted at Claris India include, but are not limited, to the following:

1. Your firm has failed to thoroughly investigate the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed [21 C.F.R. § 211.192].

a. The complaint investigation discussed in the undated report submitted with Claris India's July 2010 response to the FDA Form 483 and titled, "Complaint Investigation Report Metronidazole Injection USP Ondansetron In 5% Dextrose Injection" (Complaint Investigation Report), is inadequate. It lacks sufficient evaluation of several complaints of intravenous (IV) bag contamination, and does not provide scientific justification and supporting evidence regarding the root cause identified. For example:

1) On April 15, 2010, your firm received a complaint from a U.S. distributor (Sagent Pharmaceuticals) informing you that Metronidazole Injection USP IV bags (lot A090744) were contaminated with a swirling mass, which the complainant identified as the fungus *Cladosporium* species. There is no information in the Complaint Investigation Report to show that Claris initiated an investigation to determine the root cause and extent of the problem until April 26, 2010, when Claris received this contaminated large volume par-enteral and examined it.

On May 5, 2010 the same customer (Sagent Pharmaceuticals) reported that another lot of Metronidazole Injection USP bags (A090742) was contaminated with fungi (*Mucor* species).

The Complaint Investigation Report does not adequately address either of this complainant's contamination findings, or the root cause of the problems. For example, your customer's test results confirmed the presence of visual contaminants without discovering any leaks in the intravenous (IV) bags. You have claimed that the uniqueness of your

firm's method to detect leaks supersedes the customer's methods. Accordingly, you disregarded their findings regarding the integrity of the IV bag because their test was not performed or supervised by your own laboratory. This does not address the presence of fungi. For instance, the investigation conducted by Sagent involving Metronidazole Injection USP bags (lot A090744) did not detect a leak on the IV bag tested (dye penetration by injection), even though fungi (*Cladosporium* species) were found inside the IV bag.

Furthermore, your firm's conclusions were based solely on the returned bags examined, and do not take into account the overall implications, extent, or root cause of the detected contamination.

In your response to this letter, include your final investigation, assessment, rational and the corrective actions implemented addressing your failure to initiate the complaint investigation promptly. Also, explain if the Dye Ingress method (Container Closure Integrity) is still used to release your IV bags to the market, or if a different method was developed as part of the investigation to detect leakage in the bags.

2) On May 6, 2010, your firm received a complaint from the (b)(4) indicating a problem when they opened a case that contained six Metronidazole Injection USP IV bags (lot A090460). The technician from the pharmacy observed that fungi were in the IV bag (as well as inside the overwrap). Claris submitted a Field Alert Report (FAR) on June 3, 2010, however, your Complaint Investigation Report indicates that no leak or contamination was found in the bags received from (b)(4). Please explain this discrepancy in your response to this letter.

3) On May 31, 2010, your customer (Pfizer) reported that Metronidazole Injection USP IV bags (lot A090722) were contaminated with fungi (*Cladosporium* species) and Gram positive bacteria (*Brevibacterium casei*). Pfizer returned 33 unopened Metronidazole Injection USP bags, but your Complaint Investigation Report failed to identify the contaminants that Pfizer visually observed in at least 31 of these bags.

4) Through its investigation your firm identified defective printing stereotypes, along with packaging, shipping, and handling as the primary root causes of the contamination. The Complaint Investigation Report, however, failed to explain why a defective printing stereo would only have affected IV bags that were returned by your customers, and not other lots produced and released for distribution. Moreover, the Complaint Investigation Report lacks supporting evidence to demonstrate that the packaging, shipping, and handling contributed to the contamination.

In your response to this letter, address those issues, and also explain why these stereotypes were being used during the manufacturing process and how the suppliers of these defective stereotypes were qualified, and provide a complete explanation of how and when Claris became aware of the defect(s). In your written response to this letter, provide specific information regarding the requalification of the printing operation, and any formal study conducted to demonstrate the new printing parameters that the response states your firm adopted will prevent recurrence of the problem.

5) Claris India acts as a contract manufacturer for IV bag products marketed by other firms, as well as a distributor of some batches under Claris's own label. Your responsibility as a contract manufacturer is to inform all of your customers of a significant production problem or possible product hazard immediately. In fact, Claris India's Quality Agreements with its customers requires that your firm notify the other party within (b)(4) business days

of any quality issues related to the product. We note that your firm received worrisome complaints of lost IV bag package integrity and contamination. Yet, the Complaint Investigation Report fails to indicate what steps Claris took to ascertain whether other customers were affected by this issue, or to notify all customers of the potential for significant contamination. Please explain how and when Claris identified and informed all customers affected by your IV bag manufacturing problems. Also include your SOP describing how you keep customers promptly informed of significant occurrences (e.g., complaints, OOS, rejections, major deviations or discrepancies, any potential product hazard), concerning the products you manufacture for them.

6) The Complaint Investigation Report also reflects a number of other shortcomings in the investigation. For example, the Complaint Investigation Report fails, among other things, to:

(a) Identify when the problems that lead to the damaged IV bags and contamination of the product started.

(b) Provide a thorough evaluation and supporting evidence regarding the origin of the contamination that extended to at least eight batches of two products - Metronidazole Injection USP bags and Ondansetron Injection USP in 5% Dextrose Injection bags. The contamination was reported through at least five complaints.

(c) Provide a rationale why other products filled in the same packaging line, with the same bags and printing process, were not affected or contaminated. Similar complaints of contamination extended to batches distributed outside the United States, but the Complaint Investigation Report provides no details of when the complaints were received, or whether an investigation was conducted.

(d) Include an evaluation of the time that elapsed between the manufacturing/filling and printing process of the different batches, and the time the contamination was detected and reported by Claris India. The investigation also lacks details regarding the number of examined lots on hand, tests performed, and the sampling plan used.

(e) Supply an evaluation of the set up process, as well as the number and type of damaged bags generated during the set up. We are concerned with your proposed identification of root causes, because it fails to explain how the sharp edges and stereos only affected the bags that complainants identified, and not any of the bags remaining under your control, or other released batches.

Your firm's response dated July 3, 2010 (July 2010 response), does not provide sufficient information regarding the aforementioned issues. Please include in your response to this letter information regarding each of the issues noted above, and include the nature and origin of contamination or leakage complaints received for lots of the same products that may have been distributed outside of the United States. In addition, please provide a summary of your shipping and handling validation studies under stress conditions.

b. Your investigation into an incident involving IV bag filling rooms and Laminar Air Flow (LAFs) losing positive pressure is inadequate. For example,

During the production of Metronidazole Injection USP bags (lot A000241) the bag filling room and LAFs – intended to provide a constant flow of clean air out of the work area to prevent potentially contaminated air from entering – lost positive pressure. Your July 2010 response indicated that your firm rejected only the bags filled after 9:30 a.m. until the line was stopped, despite the fact that in the same response, your firm indicated that the last acceptable positive pressure was at 9:21 a.m. The deviation report, however, failed to provide an adequate rationale for not rejecting all the bags at risk. Specifically, the July 2010 response indicates that the reason for not rejecting the bags filled after 9:21 a.m., which potentially could have been affected, was because the microbial environmental monitoring results were within acceptable limits. This approach, however, is unacceptable because the loss in pressure may also have affected the accuracy or reliability of the environmental monitoring results; there is, thus, no assurance that all bags filled after 9:21 a.m. were unaffected by the loss of positive pressure, and therefore free of microbial contamination.

Your written procedures related to bag filling and environmental monitoring should be revised. They should ensure that all units of drug products filled between the time the last acceptable differential pressure reading was obtained, and the time the room returns to acceptable conditions, be rejected.

As noted above, we are concerned about the inadequate investigation into the contamination of your IV drug products, process deviation, and the inappropriate documentation practices cited during this inspection. Please provide a corrective action plan that describes your revised procedures, corrective and preventive actions, and controls to ensure product quality.

This plan should include a comprehensive retrospective review of your root cause analysis and the effectiveness of your corrective/preventive actions of the contamination in your drug products, raw material suppliers, equipment adequacy, sterilization cycles, and cleaning and maintenance procedures implemented to ensure that all products produced and released by your quality unit meet specifications. It should also include an evaluation of the independence, authority, and effectiveness of your firm's quality unit to rapidly address significant manufacturing issues. A robust quality unit will be essential for your firm to address any emerging or ongoing manufacturing issue in the future, and prevent the distribution of adulterated product.

2. Your firm does not have adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess [21 C.F.R. § 211.100(a)]. For example:

The inspection revealed that your firm fails to have a procedure or process in place to evaluate in-process units that are rejected due to defects during the filling of Metronidazole Injection USP bags. In fact, the investigators documented that for Metronidazole Injection USP bags (lot A000247), 48 rejections occurred during the filling process. No deviation was documented and no investigation was conducted, and you have not documented whether or not the rejected units were caused by a significant process deviation that directly affects the integrity of the other IV bags in the production lot.

Your July 2010 response is inadequate because it fails to include your rationale for releasing production lots with unexplained deviations, on the basis that the filling yield was found within limits.

Please provide a retrospective analysis of the in-process and finished units of Metronidazole

Injection USP bags, Ciprofloxin Injection USP bags, and Ondansetron Injection USP bags that were rejected due to defects found during your filling, printing, and packaging operations. Include the amount of defective units in this analysis. We also recommend that an adequate timeframe be considered for this study to enable you to establish trends regarding the amount and type of defect, and amount of rejected units per batch. Provide information on the type of defects identified, and the corrective and preventive actions implemented.

3. Your firm failed to assure that equipment used in the manufacture, processing, packing, or holding of a drug product is of appropriate design for its intended use [21 C.F.R. § 211.63]. For example:

The calibration of thermocouples (TCs) used during the validation of your terminal steam sterilizers is not performed before or after the autoclave cycles. Your response failed to provide data to support that the TCs used during the validation runs are within acceptable calibration range. The calibration of these TCs provides assurance of an accurate reading of the temperature in the sterilizer. Please provide your sterilization cycle summary for all the terminal sterilizers and cycles used by your facility, with the appropriate parameters and conclusion of the data generated.

4. Your firm has not established appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 C.F.R. § 211.113(b)]. For example:

The written procedures related to the production simulations – “media fills” - conducted to validate your capability to aseptically produce small volume parenteral (SVP) were found to be inadequate. The media fills for this line did not represent actual operations used in the aseptic production of ampoules and vials. For instance, the media fill performed by your firm in October 2009 failed to simulate the interventions performed in actual, routine production. For example, a routine production of a (b)(4) Injection vials lot would take approximately (b)(4) hours to be filled. Your written procedures (reflected in production protocols and batch record forms) for routine production require that an intervention take place every (b)(4) minutes for fill-weight verification measurements. Our review found, however, written procedures for the media fill simulation (reflected in media fill protocol), require performance of this fill-weight verification measurement only (b)(4) times throughout the media fill process. In your response to this letter, provide the finalized protocol and the summary report including all data generated during the execution of this media fill.

5. Your firm does not clean and maintain equipment at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug product [21 C.F.R. § 211.67(a)].

During the inspection the investigators observed three dispensing vessels used in the step prior to terminal sterilization that were labeled clean, however, the vessels had liquid residue inside. Your response indicated that this liquid is from final cleaning with (b)(4) rinse. The presence of liquid residue in a vessel (labeled as clean) that is later used to manufacture sterile drug products is unacceptable. In your response to this letter, provide the production lot numbers that included use of these vessels. Additionally, provide documentation to support that your firm’s cleaning procedures and practices are adequate to prevent contamination of your products. Lastly, provide the investigation report with your findings including the cleaning methods performed, as well as the corrective and preventive actions for all of your other equipment.

6. Batch production and control records prepared for each batch of drug product produced do not include complete information relating to the production and control of each batch [21 C.F.R. § 211.188]. For example:

Your firm failed to exercise adequate control over issuance of production batch records. The inspection revealed that not all pages of the batch record used in the production area are stamped and dated when issued. The purpose of this requirement is to ensure that the correct master production record is used to produce the batch record. There should be procedures and controls in place to maintain the batch record during the manufacturing of your drug product. In your response, provide your established procedures regarding issuance of batch records to provide assurance that appropriate controls are implemented, and that all the accurate pages of the issued batch records and other records are used.

FIELD ALERT REPORTING VIOLATIONS

FDA “Field Alert” reporting requirements require applicants to submit certain information about distributed drug products, including information concerning bacteriological contamination, any significant chemical, physical, or other change or deterioration product, or any failure of a distributed batch to meet the specifications established for it, to the appropriate FDA district office within three working days of receipt by the applicant [21 C.F.R. § 314.81(b)(1)]. The regulation helps establish an “early warning system” by requiring that applicants bring significant problems to the Agency’s attention promptly in order to prevent potential safety hazards from drug products already in distribution and also to prevent potential safety hazards with drug products manufactured in the future.

Based on the observations and information obtained during the inspection, Claris failed to submit Field Alert reports as required by 21 C.F.R. § 314.81(b)(1)(ii). For example:

- a. Your firm received visibly contaminated Metronidazole Injection USP bags (lot A090744) on April 15, 2010. The field alert report submitted to FDA was dated May 6, 2010.
- b. Your firm received a contaminated sample of Metronidazole Injection USP bags (lot A090460) on May 6, 2010, but the field alert report was sent to FDA on June 3, 2010.
- c. Your customer ((b)(4)) found three instances of a leaking bag with possible microbial growth of Metronidazole Injection Solution Bag and reported this to Claris India on May 20, 2009 (lot A080758), November 10, 2009 (lot A080784), and May 4, 2010 (lot A080765). None of these complaints were sent to FDA.

UNAPPROVED NEW DRUGS VIOLATIONS

Observations and information obtained during the July 2009 and January/February 2010 inspections, and review of labeling, further indicate that Claris, including by and through its wholly-owned subsidiary Claris U.S., has marketed an unapproved new drug in violation of the Act. Specifically, information obtained during those inspections indicates your firm has marketed the following prescription drug:

- Sodium Bicarbonate Injection (8.4% w/v; 250 mL and 500 mL glass vials)

As labeled, the above product is a drug within the meaning of section 201(g)(1)(B) and (C) of the Act [21 U.S.C. § 321(g)(1)(B) and (C)], because it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and it is intended to affect the structure of function of the body. Further, this drug product, as marketed by your firm, is a “new drug” within the meaning of section 201(p) of the Act [21 U.S.C. § 321(p)], because it is not generally recognized as safe and effective

for its labeled uses. Under sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(d) and 355(a)], a new drug may not be introduced or delivered for introduction into interstate commerce unless an application approved by FDA under either section 505(b) or (j) of the Act [21 U.S.C. § 355(b) or (j)], is in effect for the product. Based upon our information, there is no FDA-approved application on file for the above product. The marketing of this product without an approved application constitutes a violation of these provisions of the Act.

Additionally, because the above product is intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, adequate directions cannot be written for it so that a layman can use this product safely for its intended uses. Consequently, its labeling fails to bear adequate directions for its intended uses, causing it to be misbranded under section 502(f)(1) of the Act [21 U.S.C. § 352(f)(1)]. Because your product lacks a required approved application, it is not exempt under 21 C.F.R. § 201.115 from the requirements of section 502(f)(1) of the Act. The introduction or delivery for introduction into interstate commerce of this product therefore also violates sections 301(a) of the Act [21 U.S.C. § 331(a)].

We acknowledge Claris's assertions of "grandfather" status and have responded to that claim in a letter to Arun Menon, President-North America, Claris U.S., dated May 27, 2010. In summary, materials submitted did not demonstrate that Claris's sodium bicarbonate injection, USP 8.4% as marketed today has the same formulation, strength, dosage form, route of administration, indication, intended patient populations, and other conditions of use as a pre-1938 product.

There was no evidence indicating your product is identical to a product, bearing labeling containing identical representations concerning the conditions of its use, that was introduced prior enactment of the Act in 1938.

The introduction or delivery for introduction into interstate commerce of misbranded products without approved new drug applications violates, inter alia, sections 301(a) and 301(d) of the Act [21 U.S.C. §§ 331(a), 331(d)]. Therefore, Claris should discontinue distributing this unapproved new drug immediately. In addition, new drugs without an approved application as required may not be lawfully imported into the United States. Therefore, new drugs without an approved application are subject to refusal of admission pursuant to section 801(a)(3) of the Act [21 U.S.C. § 381(a)(3)].

We request that you outline the action Claris is taking to discontinue the marketing of this unapproved new drug product. Also please note that if you are no longer marketing this product, you must update the drug listing files in accordance with 21 C.F.R. § 207.30(a)(2).

ADVERSE DRUG EXPERIENCE REPORTS

Section 505(k)(1) of the Act [21 U.S.C. § 355(k)(1)], and 21 C.F.R. §§ 314.80 and 314.981, require an applicant to establish and maintain records and make reports to FDA of adverse drug experiences, along with certain other data or information. Failure to comply with section 505(k) of the Act is a prohibited act under section 301(e) of the Act [21 U.S.C. § 331(e)]. In addition, section 310.305 of FDA's regulations, [21 C.F.R. § 310.305], requires manufacturers, packers, and distributors who market prescription drug products that are not the subject of approved drug applications, to establish and maintain records and make reports to FDA of serious, unexpected adverse drug experiences associated with the use of their drug products.

During our July 2009 and January/February 2010 inspections of Claris U.S., FDA investigators identified violations of post-marketing adverse drug experience reporting regulations of Title 21, Code of

Federal Regulations Parts 310 and 314, and section 505(k)(1) of the Act [21 U.S.C. § 355(k)(1)]. We acknowledge the responses, dated August 12, 2009, October 7, 13, and 30, 2009, and February 24, 2010, from Arun Menon, President of Claris U.S., to the FDA Form 483s issued following the inspections, and Claris's stated commitment to developing and implementing adequate written procedures, including a number of promised additions and changes to Claris India procedures (SOPs) for handling ADE reporting. Indeed, information obtained from the inspections and the Claris responses also indicates that Claris India and Claris U.S. have shared responsibility for activities involved in meeting their ADE reporting obligations under FDA regulations. Claris also indicated certain activities have been transferred to an independent contractor, (b)(4). We note, however, that Claris has not provided all of the SOPs noted in its correspondence and, hence, the revised procedures for certain ADE reporting activities remain unclear. We request that Claris meet with FDA staff to discuss a resolution to this situation.

CONCLUSION

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations. If you wish to ship your products to and distribute them in the United States, it is the responsibility of your firm to ensure compliance with all U.S. standards for CGMP and all applicable U.S. laws and regulations.

You should take prompt action to correct the violations cited in this letter. Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, until such time as your manufacturing practices are verified to comply with CGMPs, your firm will remain under FDA Import Alert, and FDA will continue to refuse admission of all articles manufactured at Claris India, Chacharwadi - Vasana, Ahmedabad, India into the United States. The articles are subject to refusal of admission pursuant to section 801(a)(3) of the Act [21 U.S.C. § 381(a)(3)], in that, the methods and controls used in their manufacture do not appear to conform to Current Good Manufacturing Practice within the meaning of section 501(a)(2)(B) of the Act [21 U.S.C. § 351(a)(2)(B)]. Failure to promptly correct violations affecting your products that are being marketed within United States commerce may also result in legal action without further notice, including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture or distribute Ciprofloxacin, Metronidazole, Ondansetron, Fluconazole, Levofloxacin, (b)(4), and provide the dates and reasons you ceased production. Please identify your response with FEI # 3004610460.

We also recommend that you contact Paul Balcer at Paul.Balcer@fda.hhs.gov, or 301-796-3525, within five days of receipt of this letter to schedule a regulatory meeting with Claris U.S. and Claris India. If you have questions or concerns regarding this letter, contact Maan Abduldayem, Compliance Officer, at the below address and telephone number.

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Manufacturing and Product Quality
International Compliance Branch
White Oak, Building 51
10903 New Hampshire Ave
Silver Spring, MD 20993
Tel: (301) 796-3916
Fax: (301) 847-8741

Sincerely,

/S/

Deborah M. Autor

Director

Office of Compliance

Center for Drug Evaluation and Research

cc: A Menon, President – North America, Claris Lifesciences, Inc.

1 Section 314.98 of the regulations requires applicants holding an approved abbreviated new drug application (ANDA) to comply with certain reporting and recordkeeping requirements of 21 CFR § 314.80.

