# Deviations and failure investigation

**by Paul Stockbridge**

**Failure, error, Out of Specification Result (OOS), Product Quality Complaint – all can (or should) trigger a Deviation Report.**

Few things in the pharmaceutical manufacturing world give rise to so much anxiety, wringing of hands, or occasionally, downright hostility (frequently directed at the Quality Assurance department) as raising a deviation. These concerns are not without considerable justification if the whole concept and handling of deviations is not truly understood. Designed and handled badly, the deviation process can result in high emotions, finger pointing, delays and, as a result, a learning opportunity can be lost. Even more importantly, the deviation process can fall into disrepute with the inevitable result that there is considerable temptation to actively circumvent the whole system.

On the other hand, a deviation system that is designed and executed properly not only helps to assure product quality, but can also allow you to learn more about your process or product, giving the opportunity to prevent a recurrence of the problem. The deviation system, along with the rest of the Good Manufacturing Practices should be viewed not so much as "regulations that have to be complied with" but rather as part of a logical Good Business System, helping to ensure that products are consistently manufactured to the required quality!

## So, how do we achieve this in practice?

Many of the major pharmaceutical companies have complex (and if designed properly, very helpful) electronic deviation reporting systems. However, the basic starting point is to develop a good, simple, user friendly deviation reporting procedure – and then follow it up with interactive, leader led, training sessions using real examples to ensure that all those impacted not only understand the system, but also understand how to identify, conduct and report the required investigations.

I have also seen companies who try to differentiate deviations into minor, major and critical and carry out different activities as a result. From my experience, this results in considerable time being spent arguing over the level of the deviation rather than spending time on the product quality related issues themselves. My advice here is to keep it simple – a deviation is a deviation and its criticality will become obvious during the investigation process and if the deviation procedure is kept simple in concept, a relatively minor deviation and its associated actions will be dealt with quickly anyway!

- ★ A deviation can be defined as "a departure from a validated process, method, system or procedure which has the potential to affect product quality, safety or efficacy"
- ★ The Deviation system should be viewed as part of a logical Good Business System, helping to ensure that products are consistently manufactured to the required quality
- ★ The basic starting point is to develop a simple, user friendly procedure – and follow it up with training sessions using real examples
- ★ The investigation process should always consider the potential to affect product quality and should lead to the true "root cause in order to enable effective "preventive actions" to be implemented

## The deviations procedure

The Deviations procedure should contain as few words as possible. (I have the distinct impression that the level of compliance with a procedure is frequently inversely proportional to the number of words in it, so - keep it simple.) Suggested contents for a deviation procedure could be as follows:

**Introduction**
Keep this simple. The philosophy of dealing with deviations should be handled during the up-front training sessions. This section should state the purpose of the procedure, should give the timelines for completion of investigations (it is a regulatory expectation and certainly good practice to ensure that all investigations and initial approval of the deviation have taken place within 28 days of discovery) and should state who has the final say over whether a deviation has in fact taken place (normally this will be an appropriately qualified member of the Quality Unit).

**Scope**
What will trigger a deviation and require formal investigation? Examples for inclusion here could be departures from:

- ★ Validated analytical methods
- ★ Validated equipment and systems

★ Validated manufacturing processes
★ Approved procedures

Additionally, the deviation investigation and reporting system can be used in conjunction with the OOS and complaints procedures, giving a single tool for product quality related investigations.

This section should also detail the personnel to whom it may apply, and also, importantly, any exclusions (for example, manufacturers of early phase clinical trial materials, whilst they should have qualified/validated facilities, may not have well defined or validated production processes, making it impossible to tell whether an excursion is a deviation or not – but that could be the subject of another article in itself).

**Definitions**
It is important here to include definitions for any "special" terms used within the procedure. An obvious one of course is the term "deviation" itself. Others should be for the terms "causal factor", "root cause", "corrective action" and "preventive action" all of which will be discussed.

**Training method**
This is where you should state how those involved with the deviation procedure will be trained, and should be linked in with the company's training procedures.

**The procedure**
The actual process of handling the deviation process must be documented here. Again, use as few words as possible. I would suggest using the old adage of "who, what, where, when and how" in this section. The use of a flow diagram is also highly recommended to aid clarity.

As a minimum, the procedure should require the following to be documented:

★ *Date and time of the deviation*
★ *Name of the initiator*
★ *Description of the deviation*

This should be short and to the point – 1 or 2 sentences at the most and should include:

Lot number;
Step number within the process;
What happened – what was deviated from.

Do not attempt to include investigational information in this section – that comes later.

**Immediate actions on discovery**
This should be completed immediately by the operator/supervisor concerned.

**Potential impact of the deviation on product quality**
**Always** carefully examine how the deviation could have affected the quality of the product involved – it's patient safety that we could be dealing with here (and I would recommend that this section be completed by production/technical staff – with coaching from the quality unit where required.)

A requirement to ensure the deviation is at least referenced in the batch documentation in the place/time within the record that it actually happened.

## The investigation

This is where most of the difficulty and confusion can occur!

I have used the terms "deviation", "causal factor", "root cause", "corrective action" and "preventive action" and I would now like to go into these in some detail:

**Deviation**
This can be defined as "A departure from a validated process, method, system or approved procedure which has the potential to affect product quality, product safety, or product efficacy." It is critical to note the word "potential" here. It may be that after formal investigation you will determine that the product has not been adversely affected, but without that formal investigation you will not know for sure – and it is important that you do.

**Causal factor**
This is what actually, physically, happened to cause the deviation to occur, for example, "the agitator motor stopped" "the conveyor belt broke, stopping the line" "the refrigeration unit failed", etc …

**Root cause**
The causal factor described what actually happened. There are many techniques to help establish root causes, the most popular examples of which are Ishikawa (fishbone) diagrams and formal facilitated "brainstorming" sessions. Whichever techniques are used however, it is important to keep asking the question "why" and to use as much supporting data as possible. To establish the root cause, you must ask the question "why" and keep asking "why" until you have come to a logical conclusion.

The MHRA have quite rightly warned against repeatedly coming to the conclusion of "human error or "lack of training" for rather obvious reasons. Whatever root cause you come to however, always carry out a reverse logic test – ask yourself the question "if this is what we think the root cause was, would it have resulted in the deviation that occurred? It can be important that you include details of the root cause investigation process in the deviation report, if necessary as a (referenced) attachment. This not only helps to demonstrate that you have taken a detailed and rational approach to the investigation but will also help future investigations in the (hopefully unlikely) event that subsequent events suggest that the original conclusion wasn't quite right …

## Actions

Having established both the causal factor and the root cause, what do you do next? I hope it goes without saying that any manufacturing deviation will prevent affected batches of product from being approved and released until the issues have been satisfactorily resolved and the product quality and regulatory compliance assured.

There are two sets of actions which must now follow (and of course be fully documented within the Deviation report):

**Corrective actions**
These need to be completed satisfactorily before any affected materials can be released/approved. There are usually at least two aspects which need to be considered under this heading:

- ★ Actions taken to correct the *causal factor* (fix the agitator motor/temperature control unit/control system/conveyor belt/printer/etc.)
- ★ Actions taken to correct any resulting problems in the affected products. This is often a much more complex issue than the above and must take into account potential effects of the deviation on product quality. There are many functions which need to be involved in making decisions relating to correcting product faults and whilst the recommendations will (and indeed should) normally come from the technical/manufacturing personnel within the company, the final decision and authorisation for such actions must come from suitably qualified and authorised members of the company's quality unit, who of course must also consult with the company's regulatory functions to ensure that the proposed actions fall within the scope of the products licences.

The role of the Qualified Person (QP) is essential here[1]. No matter whether the deviation has occurred within the manufacture of an Active Pharmaceutical Ingredient or final Medicinal Product, the responsible Qualified Person (QP) must be fully informed about the deviation and must make the final decision over the fate of affected materials.

If particularly complex issues have arisen, it is also recommended that the company (usually the QP or his management) discuss the deviation and its associated investigation and actions with its GMP inspector. It is certainly much better to discuss serious matters prospectively with the inspectorate rather than 18 months or so later during an inspection. Whilst the inspectors will not tell you what to do (you cannot expect them to solve your problems for you) from my experience they will certainly be most helpful in assessing your own proposals and making further suggestions, particularly where there is a critical need for the product.

**Preventive actions**
As well as detailing the corrective actions described above, a deviation report must also list preventive actions. These are also sometimes known as "Actions to Prevent Recurrence" and must address the root cause identified at the conclusion of the investigation process. This is where the company can reap real rewards from the deviation system. Whilst it may be possible (and indeed in some circumstances essential) to implement some preventive actions at the same time as corrective actions, it is not uncommon for these to take much longer to put in place. The deviation procedure must require a date for such actions to be completed. As a result, it is possible that they may be given a lower priority compared with more immediate needs and, at worst, forgotten with subsequent disastrous effects.

## Quality management metrics

There are several ways to ensure that preventive actions are not forgotten:

- ★ Place affected materials "on hold" until all identified actions, including both corrective and preventive actions, have been completed. This is often not necessary from a product quality perspective and in a lot of cases will be very

unpopular with the company marketing and financial management.

Include metrics relating to deviations in the company quality management review system (deviation review is also a requirement of the Annual Product Review which is now a requirement of both the EU and US regulations[2,3]) - and ensure that there are appropriate quality measures included in all relevant personnel objectives (and I don't just mean for the QA group. Quality related metrics should be included in the objectives for all staff who have product responsibility, including production, technical, engineering, facilities management, supply chain, etc.) I would suggest that appropriate metrics relating to deviations could include:

- ★ Number and percentage of deviations open beyond 28 days of initiation
- ★ Number and percentage of preventive actions not completed within their target closure date.
- ★ Number of recurring deviation root causes (helps tell you whether the preventive actions have been taken or are effective)

## General advice

It is important that deviation reports should always "stand alone" and should be written in such a way that they provide sufficient information to "tell the story" without the use of emotional statements, in such a way that they could be understood by someone not directly familiar with the process. Don't forget that they may be read by people external to the company, a couple of years after they have occurred, and the people involved may not be available to explain.

Remember, the completion of deviations should be a "team effort" between the relevant operating departments and the quality unit – always seek QA advice and help, that should be part of their role within the company – and the QP needs to know.

## Conclusion

Dealing with deviations can never be described as a pleasant experience. However, I hope that you can see from the above, that with a well structured procedure and appropriate training, together with a logical investigation and a disciplined approach to implementation of corrective and preventive actions, that not only will your company remain within the requirements of GMP but it will also benefit from a greater knowledge of its processes and systems. As an added benefit it could also benefit financially by producing quality products that are "Right First Time"

## References

1. EudraLex, The Rules Governing Medicinal Products in the European Union. Volume 4 - Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice. Chapter 1 "Quality Management" http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/2005_10_gmp_part1_chap1.pdf
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3. US FDA 21 Code of Federal Regulations Sub Part J - Records and Reports 211.180(e) http://www.fda.gov/cder/dmpq/cgmpregs.htm

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