

# Exception Reports in Life Sciences

This Statement is intended to provide guidance and understanding of the application and use of Exception Reports within the regulated Life Sciences industry:

## What is an Exception Report?

An Exception event is an event which is generated from an automated system, when the defined parameters monitored by that system are outside specified limits. For example:

A temperature set point for a reactor is 40DegC. The specified limits within the system are set at (Low Limit) 37DegC – (High Limit) 43DegC. If the temperature is recorded at 45DegC, then this excursion from the specified limits would be recorded in an Exception Report

The Exception Report should be generated from the automated system that is monitoring and recording all the significant exception events from the manufacturing process. The same applies for any configurable or discrete excursions, such as alarm conditions that are outside the normally expected events including any comments recorded against a data entry in the exception report.

Exception Reporting is generally used where corrective action is required based on excursion from normal operating conditions. This is the primary benefit of Exception Reports, to filter information and highlight only the excursions from normal operating limits. Where an exception report is produced on a real time basis, this adds the benefit of allowing real-time reaction to an unexpected event. In summary, an exception report is a streamlined report identifying and detailing process parameters that are outside specified limits and/or actions / events not performed as specified.

It is worthwhile to explicitly mention that exception reports should be part of an overall alarm management strategy and that other alarm types should be distinguished from exception reports. If the automated system has other things which are recorded or reported which are notifications without potential product quality implications, one would not want them misconstrued as exception reports.

## What is recommended use of Exception Reporting in Life Sciences?

In Life Sciences and from a business perspective, Exception reporting is not an end in itself but should be implemented to meet clearly stated business goals. In this regard Exception Reporting is used commonly as a tool to focus the review of electronic batch records. The business value of exception reporting is that it rapidly highlights to the Quality reviewer one of the most critical elements of batch review – the exceptions.

The level of review of the full electronic batch record can vary based on the exceptions as well as the level of confidence and experience with a particular process. For new or highly variable processes, review of the full batch record is appropriate. If a process is mature, highly repeatable, and the exception reporting system has been validated as an accurate indicator of batch quality, then an appropriate review of the electronic batch record might be simply the batch exceptions, and supporting information and data. The option of first reviewing the exception report to ascertain if there were any exceptions from normal operation prior to more detailed reviews, provides Quality reviewers a mechanism to tailor review rigor to the risk of potential adverse impact to batch quality when a high level of confidence and assurance in the Exception Report being an accurate indicator of the quality of the batch exists. It is feasible that if there are no exceptions from normal operation then the batch file review can be expedited using the exception report.

It is for the quality organisation within the Life Sciences Company to decide to what extent Exception Reporting is acceptable in the review of a batch. There are two business uses of Exception Reporting within Life Sciences that need to be addressed:

1. Electronic Batch File Review by Exception
  - a. Definition – The Review of an electronic batch file by reviewing only events and data that are outside the normal specified operating parameters of the batch.
2. Batch Release by Exception
  - a. Definition – The Approval and release of a batch to the supply chain based on the review of exceptions and the approval of the remedial action taken and events recorded to indicate that all exceptions have been mitigated and that Quality Control testing is within specified limits to allow the batch to be approved.

After testing and validating the source automated system and the output Batch Exception Report to ensure functionality meets the business and regulatory requirements as per cGMP, it is possible for the business to justify that the Exception Report is sufficient evidence to show whether any adverse excursions occurred during production of the batch and batch file review by exception can be supported.

Experience within the Life Sciences industry has shown that a full review of the batch file takes place until the Quality organisation gains sufficient confidence that the Exception Report is robust enough to allow approval of the batch file. This is only possible when the Quality organisation is satisfied that no exceptions means that the batch was executed within the normal operating limits and meets the requirements of cGMP and the exception report is sufficient to allow approval of a batch. This culminates in the full trust that the system producing the Exception report has been validated and operationally challenged to an extent where review of the Exception Report provides

equivalent confidence as a full review of the electronic batch record by the Quality Organisation. Hence it is recommended that a risk assessment is carried out against possible exception events with clear mitigation of corrective actions (exception handling) agreed by the business and the Quality organisation for any event occurring. From the quality perspective these events need to be monitored over time/or number of batches to verify whether there is a trend or once-off non-conformance; the 'demonstration of compliance'. If the event is of a critical nature, the frequency of minor events is too great, or the trend is significant then Preventative actions need to be developed. Exception Handling is a fundamental part of the Exception Report in that there must be a clear process for compliance management by taking and recording appropriate corrective and preventative actions as a result of the exception.

### How can quality review the Batch Record using Exception Reports?

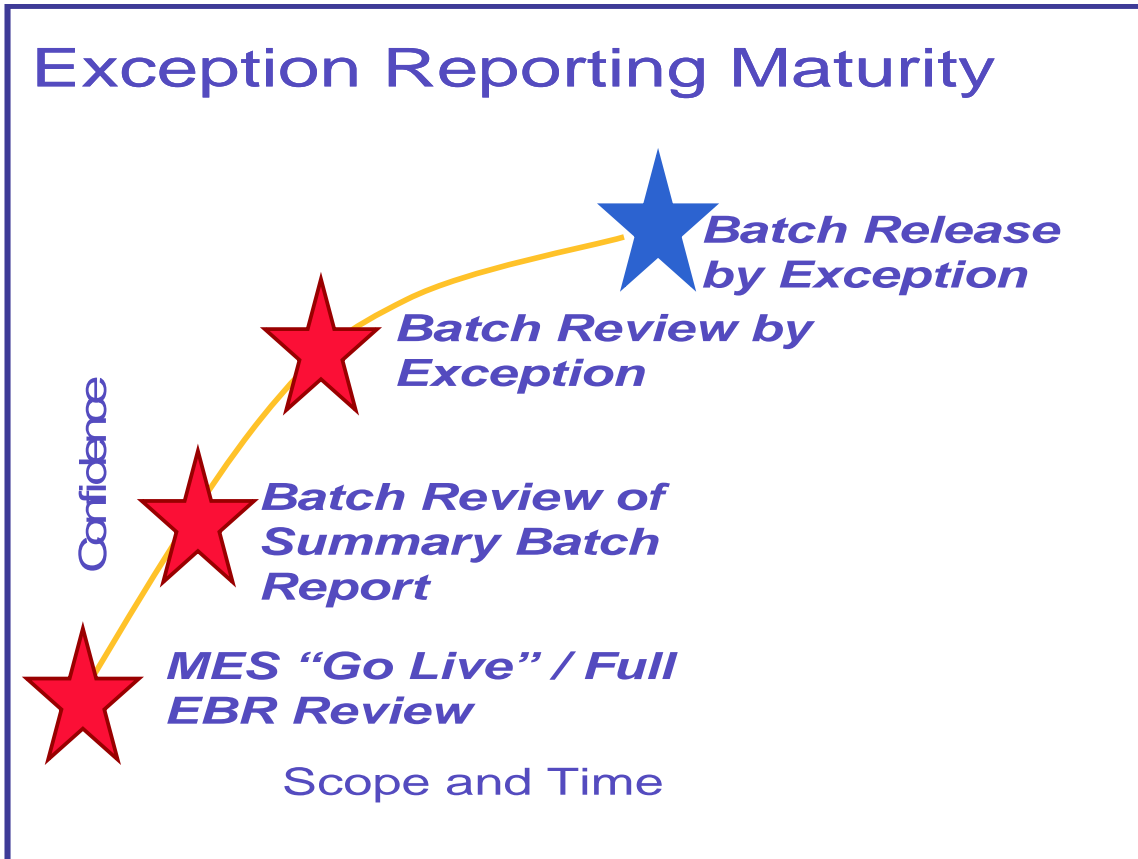
The Electronic batch file review can be expedited by forgoing a line by line review of the electronic batch record. The following steps are recommended for the review of the electronic batch file. This is an example of where Exception reports can be used in the Batch File review process:

1. Review of Batch file Exception Reports
2. Review summary Batch Report (inc. all Critical to Quality Parameters min/max/average, summary of manufacturing steps)
3. Review full electronic Batch File (inc. all manufacturing steps, events, data, signatures, comments) (As deemed necessary based on the outcome of steps 1 & 2)

It is a Quality organisation decision to ascertain what level of review of the electronic batch file is required. With this example it is clearly shown that there are differing levels of granularity from reviewing the Exception Reports to reviewing the complete electronic Batch File. It can be said the Step 1 review is mandatory and that following further steps be based on the level of exceptions. The Full review of the batch file should only take place if specifically required such as on indication of a critical excursion within the exception report or as precautionary during the introduction of a new product to the manufacturing process, or any scenario were the risk to product quality is high triggering a detailed review; however it is important to indicate that the full batch file review is entirely optional.

Forward looking statement on the feasibility of Batch Release by exception:

Batch Release by Exception is a goal to be achieved within the Life Sciences industry. However industry indication is that exception based reporting as the only review for releasing a batch has not yet been demonstrated to meet the requirements of cGMP and as such is unlikely to be acceptable at this time to the regulator. The below diagram outlines the maturity of Exception Reporting within an operating facility with the ultimate goal being the ability to release batches based on exception.



Author – Mark McKechnie – Merck Sharp & Dohme

Key Contributors to this document:

David Sheppard – Bausch & Lomb

Marian Phelan – Merck Sharp & Dohme

Paul Murray – Cordis J&J

Joe Duggan – Schering Plough

Catherine Dooley – Schering Plough

John Dietrick - Merck & Co.

Paul Walsh – Boston Scientific

James O'Sullivan – Menawat & Co.

Barry Malone – Merck Sharp & Dohme