## 1 Purpose

The purpose of this Guideline is to provide requirements for the content, scope and procedures for developing Annual Product Reviews and Product Quality Reviews, and also to outline recommendations on how to achieve compliance.

## 2 Scope and Applicability

This Guideline is applicable to all manufacturing sites sourcing Active Pharmaceutical Ingredients, Bulk Formulated Products, Drug Products and Finished Products to the US or EU, or manufactured within EU but for export only.

## 3 Definitions

### 3.1 Annual Product Review (APR)

An evaluation, conducted at least annually, to assess the quality standard of each drug product with the objective of verifying the consistency of existing process and the appropriateness of current specifications, and to highlight any trends, in order to determine the need for changes in drug product specifications or manufacturing or control procedures.

The Annual Product review is concerning drug products intended for the US market.

### 3.2 Product Quality Review (PQR)

Regular periodic review, normally conducted and documented annually, of an API, Bulk Formulated Product, Drug Product or Finished Product intended for the EU market or manufactured within EU but intended for export only, with the objective of verifying the consistency of existing process and the appropriateness of current specifications, to highlight any trends and to identify both product and process improvements.

For Bulk Formulated Product, Drug Product or Finished Product, the review includes verifying the appropriateness of current starting material specifications as well.

### 3.3 Intermediate

A material produced during steps of the processing of an API, which must undergo further molecular change or purification before it becomes an API.

### 3.4 Bulk Intermediate

A material produced during steps of the processing of a Drug Substance/API, which must undergo further molecular change or purification before it becomes a Drug Substance/API.

 

This is generally not acceptable for a drug product; manufacture has to be done according registered manufacturing specifications.

### 3.13 Level 3 Deviation

A deviation from GMP or procedure with no impact on product quality.

### 3.14 Level 2 Deviation

An isolated event or deviation from an agreed/approved procedure or process that normally results in a rapid corrective action or establishment of such corrective actions. Alternatively, a level 2 deviation may arise as a consequence of numerous repeated level 3 deviations.

### 3.15 Level 1 Deviation

A deviation that may have an actual or potential adverse effect on product quality (inc. purity and identity) safety or efficacy. Alternatively, a level 1 deviation may arise as a consequence of numerous repeated level 2 deviations.

## 4 Responsibilities

It is the responsibility of each site performing product reviews to have procedures and systems in place describing the preparation, approval and publication of product reviews.

Where applicable, a Lead Team/Site or other responsible unit must assure that Contract Manufactures and Contract Laboratories to fulfill the requirements in this guideline.

## 5 Guideline

### 5.1 Introduction

Product reviews are required to confirm the continued suitability and reproducibility of manufacturing and control processes, or alternatively to recommend any changes required to procedures, methods or specifications. They are therefore an integral part of the ongoing validation and provide a mechanism to help highlight any requirements for changes and revalidation.

### 5.2 Scope of the Product Review Report

The scope and set up of the Product Review report can be different depending on which product and market it is covering. Below is some guide to this:
The Product Review report covering US products (Bulk Formulated Products, Drug Products and Finished Products) should be product or product family specific.

 

| | | API for EU/ US | Bulk Formulated Product/ Drug product for US | Bulk Formulated Product/ Drug product manufactured in or for EU | Finished Product Packaging in or for EU |
|---|---|---|---|---|---|
| 5.4.1 | Summary | √ | √ | √ | √ |
| 5.4.2 | Batches reviewed | √ | √ | √ | √ |
| 5.4.3 | Starting / Packaging Materials | | | √ | √ |
| 5.4.4 | Analytical data | √ | √ | √ | √** |
| 5.4.5 | Changes | √ | √ | √ | √ |
| 5.4.6 | Stability data | √ | √ | √ | √* |
| 5.4.7 | Deviations | √ | √ | √ | √ |
| 5.4.8 | Reprocessed and reworked batches | √ | √ | √ | |
| 5.4.9 | Rejected batches | √ | √ | √ | √ |
| 5.4.10 | Complaints | √ | √ | √ | √ |
| 5.4.11 | Recalls | √ | √ | √ | √ |
| 5.4.12 | Returned and Salvaged goods | | √ | | |
| 5.4.13 | QA Agreements | | | √ | √ |
| 5.4.14 | Qualification status of relevant equipment and utilities | | | √ | √ |
| 5.4.15 | Market Authorization variations submitted / granted / refused | | | √ | √ |
| 5.4.16 | Post marketing commitments | | | √ | √ |
| 5.4.17 | Other | ** | ** | ** | ** |
| 5.4.18 | Comparison with previous review | √ | √ | √ | √ |
| 5.4.19 | Conclusions and recommendations | √ | √ | √ | √ |

* For primary packaging and other packaging steps that could affect product quality

** If applicable

Sections of the product review could be combined when practical.
Regular trend reports produced for other purposes (for deviations, complaints, stability, validation, etc.) could be referenced. Critical trends and conclusions from these should be evaluated with all other information in the Product Review.

 

investigations must be included in the review. Include at least Level 1 deviations in the review process. Include trending of Level 1 and Level 2 deviations.

For EU supplying sites, include a review of the effectiveness of resultant corrective and preventive actions taken. This could be reviewed as part of regular deviation trend analysis and a reference to such report included.

### 5.4.8 Reprocessed and reworked batches

All batches reprocessed and reworked must be included in the review. The reason for reprocessing or reworking and the success of procedures undertaken must also be reviewed.

### 5.4.9 Rejected batches

A listing of all batches rejected, (either from failing to meet established specification, in-process testing or other reasons), must be compiled. The reason for the rejection must also be included. Conclusions must be drawn relating to underlying trends for rejections. Established specification is the external registered specification.

### 5.4.10 Complaints

All complaints reported during the period of review must be categorized, (i.e. medical, quality of manufacture, justified/not justified etc.),and an evaluation undertaken of any trends or links to a common cause. This could be reviewed as part of regular complaint trend analysis and a reference to such report included.

A comparison of numbers and category with the previous review must be undertaken. Any remedial actions ongoing or further recommendations must be highlighted.

Product Defect Notifications raised by other sister sites and affecting the drug product must be included in the review.

### 5.4.11 Recalls, Stock Recoveries, Field Alerts

Recalls, stock recoveries and Field Alerts (for US products only) must be included in the review. Include all investigations in the review.

### 5.4.12 Returned and Salvaged goods

A list of all returned and salvaged US product lots including each lots final disposition must be included in the review.

### 5.4.13 QA Agreements

For EU supplying sites, include a review of QA Agreements with Contractors of

 

Contractor in the Product Review.

If a sponsor manufacturing site and a contractor both are supplying the same API or drug product the review must cover this fact, see also section 5.4.2.

## 5.6 Product Review SOP

### 5.6.1 Content and format of the Product Review Report

It is recommended to include templates in the product reviews SOP to support complete and consistent reports. It is recommended to write the product reviews in English, but at least the summary section must be written in English.

The SOP should for example define where raw data is to be filed, which standard regular reports can be used, etc.

### 5.6.2 Review, Approval and follow-up of actions

Formal review and acceptance of the product reviewôs content, conclusions and recommendations should be jointly undertaken by the site Manufacturing, Technical support and QA managers, or delegated senior manager within these functions. The responsibility for the final approval of product reviews lies with the QA manager or the Qualified Person.

An agreed action plan, including names and target dates should be generated and there should be a follow up process to track agreed action to completion.

### 5.6.3 Archiving

The Product Review report should be archived by QA and kept for local use only, for example during an authority inspection. It is not intended for submission to authorities.

 