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## **Reflection paper on a proposed solution for dealing with minor deviations from the detail described in the Marketing Authorisation for human and veterinary Medicinal Products (Rev1)**

### **Background**

The Directives 2001/83/EC, 2001/82/EC and 2001/20/EC, require the Qualified Person (QP) to certify that each batch of medicinal product has been manufactured in accordance with the requirements of the marketing authorisation, or in the case of investigational medicinal products, in compliance with the information provided in the request for authorisation to conduct a clinical trial. From time to time, minor manufacturing deviations from the details set out in the Marketing Authorisation or clinical trial application, which have no risk to public health, do occur. These may be one-off issues, or they may affect more than one batch. The issue is whether a QP may certify and thereby allow the release of such batches. No harmonised approach has existed hitherto for dealing with this in the European Community.

The proposal deals with the one-off type of deviations in the manufacturing process and/or analytical control methods. Recurrent deviations and deviations from other aspects of the Marketing Authorisation dossier or clinical trial application, although some of these may also be judged, on a case-by case basis as minor, are outside the scope of the proposed solution. Planned deviations are subject to controls within the manufacturer's Pharmaceutical Quality System, which should take account of the regulatory impact of the deviation, and, whether a variation is required before the deviation is implemented. Planned deviations are therefore also outside the scope of this paper.

From the side of the marketing authorisation holders and clinical trial sponsors, better communication between regulatory affairs departments and manufacturing operations with respect to the level of detail provided in marketing authorisation applications or clinical trial applications should be put in place to minimise future occurrence of deviations that are caused by unnecessary detail. It should be noted that details that fall within the scope of GMP are inappropriate for inclusion in submissions. Updates to detail in the dossier, including removal of unnecessary detail, may be provided as variations.

The proposal does not undermine the obligation of a manufacturer to manufacture each batch in accordance with the details of the marketing authorisation or clinical trial application and aims to continue the involvement of the Competent Authority when appropriate.

This Reflection Paper has been revised to take account of comments made and experience gained. It has been done to improve understanding based on feedback from industry and regulatory authorities. A number of comments from this feedback were received that cannot be taken forward at this time but may be addressed in the forthcoming revision of the Variations legislation.

### **Proposal**

Whereas:

- The safety, well-being and protection of the patient are responsibilities of every marketing authorisation holder, manufacturer and distributor.
- Pharmaceutical manufacturers must ensure that all medicinal products are manufactured in line with the details submitted in the marketing authorisation dossier and approved by the EMEA/National Competent Authority, and to ensure the safety, quality and efficacy of the product.

- Every pharmaceutical manufacturer is obliged to employ a QP who takes this responsibility.
- Every pharmaceutical manufacturer is obliged to comply with GMP and have appropriate systems and procedures for dealing with deviations and changes.
- Any deviation/non-compliance, which may materially affect the Safety or Efficacy of a batch of product, or compromises the overall product quality, must result in a QP decision not to release that batch.
- Recurrent deviations from the manufacturing process and/or analytical control methods as approved in the Marketing Authorisation or clinical trial application dossier, even though judged minor, are changes and variations to the affected Marketing Authorisations are necessary.
- Standard operating procedures and details on makes and models of equipment submitted with a Marketing Authorisation application are not considered as particulars that define the requirements of that marketing authorisation.
- It is in the interests of patients, authorities and manufacturers to ensure that there is a simple and pragmatic approach to dealing with exceptional, unplanned and one-off deviations to the manufacturing process and/or the analytical control methods.
  - Decisions based on such an approach must be under the responsibility of a QP. Where more than one QP is involved information on deviations, including those subject to this reflection paper, must be communicated to the QP responsible for certification of the batch in question. This should be included in written agreements between the QPs as referred to in Chapter 7 and Annex 16 of the GMP Guide.
  - Quality Risk Management principles must be applied in these cases (ICH Q9).
  - The decision must be supported by documentation as required by GMP and made available to the Competent Authorities on request.

Taking into account the details described above it is proposed that a batch of finished product can be considered to continue to meet the requirements of the marketing authorisation when:

1. The deviation is minor, one-off and unplanned in nature and relates only to the manufacturing process and/or the analytical control methods of either the starting materials or the medicinal product as described in the Marketing Authorisation or clinical trial application and has no influence on the result of analytical testing.
2. The active substance and finished product specifications as described in the marketing authorisation or clinical trial application are complied with.
3. An assessment is performed by the manufacturer using an appropriate approach such as described in ICH Q9, Quality Risk Management, to establish and support a conclusion that the occurrence is a minor quality deviation that does not affect the safety and efficacy of the product.
4. The risk assessment should assess the need for inclusion of the affected batches in the on-going stability programme as required by Chapter 6 of the GMP Guide.
5. The risk assessment for biological medicinal products should consider in particular that even minor changes to the process can have an unexpected impact on safety or efficacy.

6. The Quality Risk Management Process is integrated into the manufacturer's Pharmaceutical Quality System, notably the documentation system established to comply with GMP, and records are available for inspection by the Competent Authorities.
7. Deviations must be properly recorded in the relevant batch documentation in accordance with GMP. All such deviations must be reviewed as part of the product quality review as required by Chapter 1 of the GMP Guide.

Trends or recurrences and other deviations from the details of the Marketing Authorisation or clinical trial application must be flagged as problems that require resolution with the Competent Authorities including, if necessary, the submission of variations. The proposed solution described above does not apply in these circumstances.