European Medicines Agency
Inspections

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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 (including biological products):

Background

The Directives on Good Manufacturing Practice (GMP), 91/412/EC and 2003/94/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. From time to time minor manufacturing deviations from the details set out in the Marketing Authorisation application, which have no risk to public health, do occur. These may be one-off issues, or they may affect successive batches. The issue is whether a QP may certify and release such batches. No harmonised approach exists 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, although some of these may also be judged, on a case-by case basis as minor, are outside the scope of the proposed solution.

From the side of the marketing authorisation holders, better communication between regulatory affairs departments and manufacturing operations with respect to the level of detail provided in a marketing authorisation application should be put in place to minimise future occurrence of deviations that are caused by such unnecessary detail. Updates to detail, including removal of unnecessary detail may be provided as variations.

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

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/NCA, 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.

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- Recurrent deviations from the manufacturing process and/or analytical control methods as approved in the Marketing Authorisation 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.

    - 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.

2. The active substance/antigen and finished product specifications as described in the marketing authorisation are complied with.

3. An assessment is performed by the manufacturer using the approaches described in ICH Q9, Quality Risk Management, to 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 Quality Risk Management Process is integrated into the manufacturer's quality assurance system, notably the documentation system established to comply with GMP, and records are available for inspection by the Competent Authorities.

6. All such deviations must be reviewed as part of the annual 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 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.

This interpretation of the requirements is published here in the form of a reflection paper and comments are invited. The European Commission is ready to support the principles being implemented as an amendment to Annex 16 of the GMP Guide depending on feedback on practical aspects. Amendments to the GMP Guide are published by the European Commission in Eudralex volume 4 following public consultation.