



**PROPOSED NEW SECTIONS FOR  
WHO GOOD MANUFACTURING PRACTICES (GMP):  
MAIN PRINCIPLES FOR PHARMACEUTICAL PRODUCTS**

***DRAFT FOR COMMENT***

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**In order to receive our guidelines electronically, if not already the case, please let us have your e-mail address (to [bonnyw@who.int](mailto:bonnyw@who.int)) which we will add to our electronic mailing list.**

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**PROPOSED NEW SECTIONS FOR  
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PHARMACEUTICAL PRODUCTS**

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Preparation of first draft working document QAS/09.330	July 2009
Discussion during consultation on WHO guidelines for medicines quality assurance, quality control laboratories and transfer of technology	27-31 July 2009
Presentation to the WHO Expert Committee on Specifications for Pharmaceutical Preparations	12-16 October 2009
Further updates: discussion at informal consultation on quality assurance systems, medicines and risk analysis	4-6 May 2010
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Presentation to the WHO Expert Committee on Specifications for Pharmaceutical Preparations	18-22 October 2010
Further action as necessary	

## **PROPOSED NEW SECTIONS FOR WHO GOOD MANUFACTURING PRACTICES (GMP):MAIN PRINCIPLES FOR PHARMACEUTICAL PRODUCTS**

### **INTRODUCTION**

Among other feedback which was discussed during the consultation on WHO guidelines for medicines quality assurance, quality control laboratories and transfer of technology on 27-31 July 2009, the need has been identified to incorporate a new section (1.4) on "Product quality review" under Chapter 1: "Quality Assurance" in the *WHO good manufacturing practices (GMP): main principles for pharmaceutical products*, which is reproduced below for easy reference.

In addition, several updates have been suggested to further enhance and include the concept of risk management, replace "drugs" by the new terminology "medicines" and newly include the concept of a "quality unit".

The guideline: WHO GMP: main principles for pharmaceutical products can be found at the following link:

[http://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/production/en/index.html](http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/index.html) → [Good Manufacturing Practices for Pharmaceutical Products: Main Principle \[pdf 632kb\]](#)

Annex 4, WHO Technical Report Series 908, 2003

The paragraphs concerned are to be found below. Text which has been changed from the original (reference as above) or which is new is **highlighted**.

## Glossary

### **quality unit**

An organizational unit independent of production which fulfils both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

## **Quality management in the drug industry: philosophy and essential elements**

The concepts of quality assurance, GMP, quality control and quality risk management are interrelated aspects of quality management, and should be the responsibility of all personnel. They are described here in order to emphasize their relationship and their fundamental importance to the production and control of pharmaceutical products.

### **1. Quality assurance**

#### 1.2

(m) there is a system for quality risk management

1.4 Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

1.5 The quality risk management system should ensure that:

- the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient; and
- the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

## **Product quality review**

1.6 Regular, periodic or rolling quality reviews of all medicinal products, including export-only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:

- (i) a review of starting materials and packaging materials used for the product, especially those from new sources;
- (ii) a review of critical in-process controls and finished product results;
- (iii) a review of all batches that failed to meet established specification(s) and their investigation;
- (iv) a review of all significant deviations or non-conformances, their related investigations and the effectiveness of resultant corrective and preventive actions taken;
- (v) a review of all changes carried out to the processes or analytical methods;
- (vi) a review of dossier variations submitted/granted/refused;
- (vii) a review of the results of the stability monitoring programme and any adverse trends;
- (viii) a review of all quality-related returns, complaints and recalls and the investigations performed at the time;
- (ix) a review of adequacy of any other previous product process or equipment corrective actions;
- (x) for new dossiers and variations to the dossiers, a review of post-marketing commitments;
- (xi) the qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc.; and
- (xii) a review of technical agreements to ensure that they are up-to-date.

The manufacturer and marketing authorization holder, where different, should evaluate the results of this review and an assessment should be made whether corrective and preventive action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Agreed corrective and preventive actions should be completed in a timely and effective manner. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection.

Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, etc., where scientifically justified.

Where the marketing authorization holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review. The authorized person responsible for final batch certification, together with the marketing authorization holder, should ensure that the quality review is performed in a timely manner and is accurate.

## 8. Self-inspection, quality audits and supplier's audits and approval

### 9. Personnel

#### Key personnel

9.6 Key personnel include the heads of production, the head(s) of quality unit(s) and the authorized person. The quality unit(s) typically comprise the quality assurance and quality control functions. In some cases, this could be combined in one department. The authorized person may also be responsible for one or more of these quality unit(s). Normally, key posts should be occupied by full-time personnel. The heads of production and quality unit(s) should be independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated.

9.7 Key personnel responsible for supervising the production and quality unit(s) for pharmaceutical products should possess the qualifications of a scientific education and practical experience required by national legislation. Their education should include the study of an appropriate combination of: ...

9.8 The heads of the production and the quality unit(s) generally have some shared, or jointly exercised, responsibilities relating to quality.

9.10 The head(s) of the quality unit(s) generally have the following responsibilities: ...

- (h) to ensure that the required initial and continuing training of quality unit personnel is carried out and adapted according to need;
- (i) establishment, implementation and maintenance of the quality system;
- (j) supervision of the regular internal audits or self-inspections;
- (k) participation in external audit (vendor audit);
- (l) participation in validation programmes.

Other duties of quality control are summarized in sections 17.3 and 17.4.

9.11 The authorized person is responsible for compliance with technical or regulatory requirements related to the quality of finished products and the approval of the release of the finished product for sale or supply.

9.12 Assessment of finished products should embrace all relevant factors, including the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product, and an examination of the finished pack.

9.13 No batch of product is to be released for sale or supply prior to certification by the authorized person(s). In certain countries, by law, the batch release is a task of the authorized person from production together with the authorized person from quality control.

9.14 The authorized person responsible for approving a batch for release should always ensure that the following requirements have been met: ...

9.15 The function of the approval of the release of a finished batch or a product can be delegated to a designated person with appropriate qualifications and experience who will release the product in accordance with an approved procedure. This is normally done by quality assurance by means of batch review.

## 12. Premises

### Production areas

12.31 Premises for the packaging of pharmaceutical products should be specifically designed and laid out so as to avoid mix-ups, contamination or cross-contamination.

## 16. Good practices in production

### Packaging operations

16.36 Production records should be reviewed as part of the approval process of batch release before transfer to the authorized person. Any divergence or failure of a batch to meet production specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.

## 17. Good practices in quality control

17.1 Quality control is the part of GMP concerned with sampling, specifications and testing, and with the organization and documentation which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. Quality control is not confined to laboratory operations, but may be involved in many decisions concerning the quality of the product.

17.3 [Item (g) has been deleted.]

17.5 [deleted.]

17.17 In lieu of full testing by the manufacturer, a certificate of analysis may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results (see sections 8.8 and 8.9) and through on-site audits of the supplier's capabilities. ...

### Batch record review

17.21 Quality control records should be reviewed as part of the approval process of batch release before transfer to the authorized person. ...