Technologies, standards and norms

Quality standards for pharmaceutical products

The WHO Expert Committee on Specifications for Pharmaceutical Preparations advises the WHO Director-General and Member States on pharmaceutical quality issues. The heightened interest in quality of medicines became apparent in the request expressed by Member States during the 2013 meeting of the World Health Assembly to hold an open session on this topic in conjunction with the 48th Expert Committee meeting. This article gives an overview of guidance adopted by the Committee at its 48th meeting, held in Geneva on 14-18 October 2013.

The Expert Committee on Specifications for Pharmaceutical Preparations

The WHO Expert Committee on Specifications for Pharmaceutical Preparations provides guidelines on a wide range of medicines quality assurance issues. This work is linked to WHO’s mandate to set necessary standards (both written and physical) that complement and improve current regulatory requirements created and applied in WHO Member States, including those developed by regional and inter-regional regulatory fora. Input from a wide range of experts from different settings, together with a global stakeholder consultation process, ensures that the guidelines are scientifically well-founded, meaningful and implementable.

In line with current regulatory concepts, the guidance aims to ensure that quality is built into a pharmaceutical product at each step of its life cycle and checked by measures such as testing to verify that all batches of finished product on the market conform to approved specifications. Accordingly the guidelines cover all areas of pharmaceutical quality assurance, from medicines design and production throughout distribution until they reach the end user.

The International Pharmacopoeia

The development of a unified pharmacopoeia was the initial scope of work of the Expert Committee when it was created at the very first World Health Assembly in 1948. The maintenance of The International Pharmacopoeia remains an important area of its work. In recent years, discussions in this area have provided a platform for renewed global efforts to harmonize the official quality specifications and test methods for pharmaceuticals across countries and regions.

At its 48th meeting the Committee adopted 16 specific monographs for inclusion in The International Pharmacopoeia, including 5 for medicines to treat neglected tropical diseases, 3 for antimalarial medicines, 3 for antiviral medicines, 2 for maternal, newborn, child and adolescent health medicines, 1 for an antituberculosis medicine, and 2 for other medicines. In addition, it adopted four general texts relating respectively to melting temperature and melting range, strengths of medicines in alignment with 1 See also the article on page 127 of this issue.
the most recent essential medicines list, dissolution testing of tablets and capsules, and reference substances and spectra.

Furthermore, the Committee endorsed the proposals made on International Chemical Reference Substances (ICRS) by the ICRS Board. It agreed to the adoption of 11 new ICRS and considered the withdrawal of 13 ICRS that no longer had a pertinent monograph in The International Pharmacopoeia.

In the area of radiopharmaceuticals WHO collaborates with the International Atomic Energy Agency (IAEA) to ensure that The International Pharmacopoeia is up to date. At its meeting the Committee discussed a workplan for adding and updating priority monographs. It also adopted a 13-step procedure for the ongoing development and revision of specifications for radiopharmaceuticals (1), ensuring that the monographs undergo thorough review and consultation as is the case for other content of The International Pharmacopoeia.

**Good manufacturing practice (GMP)**

Compliance with GMP is a fundamental requirement that must be met in any pharmaceutical quality assessment process. GMP applies to the entire manufacturing chain of innovator and generic products.

The Expert Committee adopted an update of the main principles of the WHO good manufacturing practices for pharmaceutical products (2). The revised text has considered all current concepts and inputs from different WHO regions and countries, including the concepts of quality-by-design, risk management and pharmaceutical quality management throughout a product’s life cycle. Together, these concepts provide for a tailored, science-based, systematic approach to pharmaceutical manufacturing and development, taking into account the critical attributes and risk factors identified for each specific product with a focus on patient safety. The revised GMP guidelines call for implementation of a Pharmaceutical Quality System (PQS) that extends to all life-cycle stages of a product, with a strong link between pharmaceutical development and manufacturing activities to facilitate innovation and continual improvement.

Furthermore, given the importance of outsourcing in the context of today’s globalized production, the revised guideline includes strengthened recommendations on the control of activities conducted by contractors and sub-contractors. Ongoing revisions of supplementary GMP and related guidelines on non-sterile process validation and on hold-time studies were also discussed.

**Model quality assurance system for procurement agencies**

Humanitarian organizations provide significant amounts of medicines for use in resource-constrained countries. Given that most of the recipient countries have limited medicines regulatory capacity, these organizations have developed their own quality assurance systems for the pharmaceuticals that they procure or fund.

At the request of international organizations WHO had developed a model quality assurance system (MQAS) for procurement agencies, which was adopted by the Expert Committee in 2006. The MQAS has become one of the pillars of medicines quality assurance by international donors and humanitarian organizations. Additional requirements are in place for antiretrovirals, anti-tuberculosis medicines and antimalarials, which must be WHO-prequalified or approved by a stringent regulatory authority.

As international organizations harmonized and strengthened their quality
assurance policies over the years, they were looking for a more standardized way to implement the MQAS principles. The guidance document was revised by a working group with representatives of 13 organizations involved in international procurement and funding of medicines. The revised MQAS guidance document (3) – including an updated model inspection report and a newly revised inter-agency product questionnaire – was approved by the Committee at its 48th meeting, together with a standardized assessment tool (4) enabling procurement agencies to assess their own systems and those of their intermediary suppliers. The revised MQAS has been described in more detail in an earlier issue of this journal.

A common interpretation of MQAS requirements will form a basis for partner organizations to share the outcomes of their assessments, thus saving resources. It will also help to entrench uniform quality requirements for donor-funded medicines. This is especially important for products such as life-saving antibiotics, which are not subject to additional quality requirements by donors but nonetheless critically important for public health.

**WHO prequalification of stringently assessed products**

The WHO Prequalification Team assesses priority essential medicines belonging to selected key therapeutic areas to establish whether they are acceptable, in principle, for procurement by international organizations. For products that are already approved by a stringent regulatory authority WHO will recognize that authority’s scientific evaluation, provided that both the manufacturer and the authority agree to share with WHO certain specific information.

At its 48th meeting the Committee adopted a revised guideline on prequalification of stringently approved products. The revised text includes the requirements for both multisource (generic) and innovator products – previously described in two separate guidelines – with a number of updates for the latter product type (5).

The principles of this guideline can be applied to other initiatives for unilateral or mutual recognition of product approval between authorities.

**Product dossier assessment: quality part**

To harmonize the format of product dossiers in submissions for marketing authorization of pharmaceuticals, ICH member countries had introduced the Common Technical Document (CTD) format in 2003. The CTD is today the required format for submissions in many WHO Member States. The Association of Southeast Asian Nations (ASEAN) has developed and implemented the ASEAN Common Technical Dossier (ACTD) format with a view to arriving at mutual recognition arrangements on product approval. The CTD is also the required format for WHO prequalification dossiers.

The “quality part” (Module 3) of the CTD is concerned with technical specifications and manufacturing processes of the active ingredients and the finished product. It is applicable both to innovator and generic products. The information provided in this part of the dossier is critical for pre-approval assessment and post-marketing control.

The WHO Prequalification Team had developed detailed guidance for applicants on how to submit quality data in prequalification dossiers in line with Module 3 of the CTD format. This guidance has been adapted further to make it suitable for wider use. A document was adopted by the Committee that describes...
harmonized, efficient processes for the development of product dossiers by manufacturers and for their assessment by NMRAs (6).

Although the guidelines reflect stringent regulatory principles they are not intended to be prescriptive. Alternative, scientifically justified approaches are acceptable, and regulatory authorities may have requirements not specifically described in this guidance.

By promoting the wide implementation of the CTD format in WHO Member States the guidance will contribute to regulatory convergence. For manufacturers it can save resources in dossier development, as they will be able to submit the same dossier to multiple regulatory authorities. For regulators it will facilitate collaboration and exchange of information, enabling them to pool their resources to control the quality of pharmaceutical products circulating in the global markets.

References


The draft versions of the revised guidelines (1-6) as posted for public comment are available at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/.