Pharmacopoeial standards

Global specifications: the example of capreomycin

Capreomycin is used to treat multi-drug-resistant tuberculosis, an increasing public health problem. The example of the new capreomycin monographs in The International Pharmacopoeia shows how international specifications can provide added value for WHO Member States, including countries with resource limitations.

Public quality control standards
Pharmacopoeial monographs can be used by manufacturers, regulators and other stakeholders for quality control of active pharmaceutical ingredients (APIs) and finished products against internationally recommended specifications. Pharmacopoeial requirements in countries form part of national legislation, defining the specifications which pharmaceutical products circulating on their market must fulfil.

The International Pharmacopoeia (1) was created to help promote harmonized and suitable quality control testing standards among WHO Member States. It aims to provide analytical tests that can be performed with the recommended equipment for first-stage and medium-sized pharmaceutical quality control laboratories (2) in all regions of the world, including remote areas.

Focus on ‘neglected monographs’
The International Pharmacopoeia focuses on essential medicines that are of public health importance in WHO Member States, and for which monographs are not available in other pharmacopoeias. An example of such a medicine is capreomycin, an aminoglycoside antibiotic discovered in 1960 and first registered in 1971. Today it is part of WHO-recommended regimens to treat multi-drug-resistant tuberculosis, an increasing public health threat in many parts of the world.

Capreomycin was removed from the British Pharmacopoeia in 2003 because of its low use in the UK. Although monographs for capreomycin are included in the United States Pharmacopeia (USP) as well as the Chinese and Indian Pharmacopoeias, WHO decided to develop a further public standard because it was felt that the available methods and specifications were not sufficient to fully characterize and standardize the quality of the substance.

Input from world experts
Experts from universities, WHO Collaborating Centres and national regulatory authorities collaborated to develop the monographs for capreomycin sulfate active substance and capreomycin injection through WHO’s defined step-wise process (3). The initial drafts underwent two public consultations, during which many valuable comments were received. The new monographs were published in the Third and Fourth Supplement of The International Pharmacopoeia respectively. Their advantages for users are outlined on the next page.
Capreomycin monographs: Added value for WHO Member States

Comprehensive description
Produced by fermentation, capreomycin is a mixture of several structurally related components and thus difficult to characterize. *The International Pharmacopoeia* is currently the only pharmacopoeia to give comprehensive information on structures, formulas, relative molecular weights and chemical names for all four major components (capreomycin IA, IB, IIA and IIB). This information facilitates the production and registration of products containing capreomycin.

Alternative options for identity test
Two alternative combinations of identity tests are provided, for users to choose the option that can be performed using the equipment that is available in the laboratory (see *Table 1*).

<table>
<thead>
<tr>
<th>Test Option 1</th>
<th>Option 2</th>
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<tbody>
<tr>
<td>A  IR Spectrophotometry</td>
<td>■</td>
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<tr>
<td>B  Thin-layer chromatography</td>
<td>■</td>
</tr>
<tr>
<td>C  Absorption spectrum of solution in hydrochloric acid</td>
<td>■</td>
</tr>
<tr>
<td>D  Absorption spectrum of solution in sodium hydroxide</td>
<td>■</td>
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<tr>
<td>E  General identification test for sulfates</td>
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First-ever pharmacopoeial test for related substances
The impurities of capreomycin affect the safety of the finished product. *The International Pharmacopoeia* describes the first-ever pharmacopoeial related substances test for capreomycin and defines acceptable limits for impurities – not an easy task, as toxicity data for old medicines like capreomycin can be challenging to put together. The test uses a high performance liquid chromatography (HPLC) method, a widely used analytical technique (see *Figure 1*).

Quantification of content
Other pharmacopoeias propose a microbiological assay, where the content of capreomycin is measured through its inhibitory effect on susceptible microorganisms. The assay in *The International Pharmacopoeia* is based on the same HPLC method as the related substances test (*Figure 1*), enabling a direct calculation of the content in terms of mass. This saves time and resources as the laboratory can perform two tests with the same analytical system.

Easy-to-use reference standard
A solution of the reference substance with a defined concentration is needed to quantify capreomycin. Capreomycin absorbs water from the atmosphere. It may therefore be difficult to weigh the substance accurately on an analytical balance.

The European Directorate for the Quality of Medicines and Healthcare (EDQM) is responsible for the establishment and distribution of WHO’s International Chemical Reference Substances. Given the importance of this project and the objective difficulty of weighing capreomycin in a laboratory, the EDQM is currently assessing the feasibility of lyophilizing the reference standard. If this is feasible, the use of the ICRS will become fairly simple i.e. just adding to the vial a predefined volume of solvent.

Quantification of capreomycin components and related substances by HPLC
The HPLC method separates the different related compounds in capreomycin sulfate according to their affinity to a lipophilic stationary phase. In the resulting chromatogram the content of each compound is proportionate to the area of the corresponding peak.

![Figure 1. Typical chromatogram showing the separation of the four main components of capreomycin sulfate (7, 9, 12 and 13) and related substances. Source: Reference (5).](image-url)

**Related substances**: The peak response areas for the impurities are compared with those of the major peaks for capreomycin IA, IB, IIA and IIB; Acceptance limits are:
- All impurities ≤ 2%
- Only one impurity between 1 and 2%
- Sum of all impurities: ≤ 7%

**Assay**: The content is calculated from comparing the four major peak areas of the test substance with those of the reference substance, which has a declared content of capreomycin IA, IB, IIA and IIB.
Supporting market entry of quality-assured products

*The International Pharmacopoeia* is aligned with the needs of the WHO prequalification programme, which assesses the quality of medicines for procurement by UN agencies and other buyers that have recognized the central importance of medicines quality not only in treating individual patients, but also in reducing the risk of resistance that could make a medicine ineffective for entire populations.

Capreomycin is invited for WHO prequalification. At the end of September 2014 the first API was prequalified, another was under assessment. The first capreomycin injection was prequalified in October 2014, with four other submissions under assessment (4). Appropriate specifications and suitable test methods will support manufacturers in achieving WHO prequalification for their products, resulting in additional quality-assured products on the global market.

Funding

In the past, the work on *The International Pharmacopoeia* used to be funded from WHO’s regular budget. This funding source has decreased to virtually zero in recent years. The activities are currently funded for the most part by UNITAID, whose financial contribution is gratefully acknowledged. In addition, WHO Member States provide in-kind contributions and support valued at a multiple of the programme’s operational budget. These contributions include activities by national quality control laboratories, national support to WHO collaborating centres, and – very importantly – time given by individual experts.

Conclusion

Quality control testing is a mainstay of pharmaceutical quality assurance in production and regulation. In providing well-designed, globally applicable specifications and test methods for widely used medicines free of charge, WHO fills a need in Member States. *The International Pharmacopoeia* is useful in development, production, registration and post-market surveillance in countries around the world, and thus helps to ensure that essential medicines used in WHO Member States meet the internationally accepted quality requirements that make them safe and effective.

References


4. WHO. List of all APIs and FPPs invited for prequalification, and number prequalified or currently under assessment per product. (25 September 2014). Available from apps.who.int/prequal - Information for applicants.