WHO Drug Information

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**International Nonproprietary Names (INN)**

93 Recommended INN: List 75

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International Conference of Drug Regulatory Authorities (ICDRA)

The 17th ICDRA will take place in
Cape Town, South Africa
27 November – 2 December 2016

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**Abbreviations and web sites**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Name of Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use (EMA)</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency (<a href="http://www.ema.europa.eu">www.ema.europa.eu</a>)</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration (<a href="http://www.fda.gov">www.fda.gov</a>)</td>
</tr>
<tr>
<td>Health Canada</td>
<td>Federal department responsible for health product regulation in Canada (<a href="http://www.hc-sc.gc.ca">www.hc-sc.gc.ca</a>)</td>
</tr>
<tr>
<td>MHLW</td>
<td>Ministry of Health, Labour and Welfare, Japan</td>
</tr>
<tr>
<td>MHRA</td>
<td>Medicines and Healthcare Products Regulatory Agency, United Kingdom (<a href="http://www.mhra.gov.uk">www.mhra.gov.uk</a>)</td>
</tr>
<tr>
<td>Medsafe</td>
<td>New Zealand Medicines and Medical Devices Safety Authority (<a href="http://www.medsafe.govt.nz">www.medsafe.govt.nz</a>)</td>
</tr>
<tr>
<td>PRAC</td>
<td>Pharmacovigilance Risk Assessment Committee (EMA)</td>
</tr>
<tr>
<td>PMDA</td>
<td>Pharmaceuticals and Medical Devices Agency, Japan (<a href="http://www.pmda.go.jp/english/index.htm">www.pmda.go.jp/english/index.htm</a>)</td>
</tr>
<tr>
<td>Swissmedic</td>
<td>Swiss Agency for Therapeutic Products (<a href="http://www.swissmedic.ch">www.swissmedic.ch</a>)</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration, Australia (<a href="http://www.tga.gov.au">www.tga.gov.au</a>)</td>
</tr>
<tr>
<td>U.S.</td>
<td>United States of America</td>
</tr>
</tbody>
</table>

**Note:**
The online version of this issue (available at www.who.int/medicines/publications/druginformation) has direct clickable hyperlinks to the documents and web pages referenced.
Concept paper for comment

A framework for risk-based identification of essential medicine products for local manufacturing in low- and middle-income countries

This is the first draft of a concept paper for discussion. It aims to provide a risk assessment strategy and aspects to consider when evaluating whether an essential medicine can be manufactured locally in low- and middle-income countries with relatively limited pharmaceutical manufacturing capability and experience.

This concept paper is part of the work that WHO is initiating, in collaboration with UNIDO, to promote quality local production of medicines in developing countries. The paper is intended to be developed into a joint document which provides guidance to manufacturers, regulatory officials and policy makers on how to minimize risk in manufacturing operations by selecting appropriate essential medicines for production in accordance with existing levels of GMP compliance, and how to tailor technical assistance to implement this approach, with the ultimate goal to eventually achieve local production of medicines by fully GMP-compliant manufacturers in developing countries. A second concept paper on Good Manufacturing Practice (GMP) road mapping is being prepared by UNIDO and will also be published in this journal for comments.

Comments and suggestions on this paper are invited to facilitate further discussion. They should be sent to druginfo@who.int.

Introduction

Background

A number of papers have been published that discuss the manufacturing of medicinal products in low- and middle-income countries (LMICs) in various contexts. These include the diseases to be treated, capacity building, access to medicines, cost, skills, training, job creation, intellectual property rights, transfer of technology, government incentives, and advantages and disadvantages (e.g 1, 2, 3, 4, 5).

At the African Union Conference of Ministers of Health, held in Johannesburg in April 2007 (6), a Pharmaceutical Manufacturing Plan for Africa was proposed: “This plan of action is being presented in phases to allow intense assessment of the feasibility and modality of local manufacturing of medicines in Africa.” The paper further suggested that “the plan must investigate and suggest criteria for determining what is to be produced.” One of the conclusions of this proposal stated: “Local production can be successfully done in the continent. However, there is need for the African countries to reassess the realities, possibilities and the feasibility of the programme so that it moves from being a political slogan to a reality after good ground work. The time needed to do thorough scientific analyses in the continent, together with WHO and other bodies that can add value, is certainly longer than two years.”

Often an assessment of what is to be produced focuses on the diseases to be treated, with little attention to the level of technology involved with respect to the development and manufacture of pharmaceutical products in LMICs. The technology level does not only
affect the feasibility of the manufacturing process, including packaging and quality control testing, but also the overall quality assurance system of the manufacturer, as well as the capacity of the local national medicines regulatory authority (NMRA) to effectively assess the resultant dossier, to conduct inspections and to regulate life cycle variations. These activities by manufacturer and NMRA are essential to ensure that the patient is getting medicines of acceptable safety, efficacy and quality, according to WHO standards as set out in WHO guidelines.

It is thus appropriate to consider the level of manufacturing technology in conjunction with the risk associated with the product itself, including the ingredients and the type of manufacture when selecting products for manufacture in LMICs.

**Purpose**

The purpose of this document is to provide a risk assessment strategy and aspects to consider when evaluating whether an essential medicine can be manufactured locally in an LMIC with assured quality, efficacy and safety. The evaluation framework can be used to help identify potential candidate products, and cascades from proposals raised in the African Union Conference of Ministers of Health in April 2007, specifically to address the need for criteria for determining what is to be safely produced.

The document is intended to serve as a reference for those that are seeking to technically evaluate or technically advise on decisions for local manufacturing of essential medicines. It is anticipated that the stakeholders and advisors will have a fundamental technical knowledge of the concepts presented but may seek the input of additional technical expertise as needed.

While the document considers technical risk assessment across the range of products on the WHO Model List of Essential Medicines (EML) and the WHO Model List of Essential Medicines for Children (EMLc) (7) it is intended to serve as a tool particularly for manufacturers in countries that do not yet have a well-established pharmaceutical manufacturing presence. Although the impetus for development of the reference originated in the African Union, it is intended that it should serve an assessment exercise in any LMIC.

This document should be read in conjunction with WHO's guideline on *Pharmaceutical development of multisource (generic) pharmaceutical products – points to consider* (8) and other development guidelines such as *Development of paediatric medicines: points to consider in formulation* (9), *ICH Q8: Pharmaceutical development* (10) and *Quality by design for ANDAs: An example for immediate-release dosage forms* (11).

**Scope**

The document provides a strategy for selection of products on the EML/EMLc that could be considered for local manufacturing in LMICs, including by manufacturers with no or limited development and manufacturing experience (start-up situations). The document presents a framework for the identification of the spectrum of risks associated with the manufacture, including packaging and testing. It presents the rationales for risk designation specifically in the context of start-up manufacturing in LMICs. The identified risks may then be considered in total to inform recommendations to move forward with subsequent stages of manufacturing development. Critical limiting risks must be evaluated on a case-by-case basis against available mitigation options for ultimate go/no-go recommendations.

The concepts presented are intended to aid evaluation of product candidates from the EML/EMLc. As such, these products include dosage forms manufactured from small molecule, synthetically derived active pharmaceutical ingredients (APIs) and are most often

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1. ANDA: Abbreviated New Drug Application (U.S. FDA)
multisource (generic) products. However, the concepts could be applied to the manufacture of innovator products produced locally, where appropriately supported by the innovator parent company.

The EML/EMLc includes biologically derived products, namely vaccines, which are manufactured in a number of countries falling within the definition of an LMIC\(^2\). As such they are in scope, and risk assessment criteria are identified in this document. Medicines not on the EML/EMLc are considered out of scope of the document, as are any products at the development stage. The manufacture of active ingredients themselves is also out of scope of this document.

Other available sources should be referenced for the evaluation of preparedness in the context of Good Manufacturing Practices (GMP) or Quality Management Systems (QMS). Similarly, criteria not related to technical and scientific factors, such as costing, profitability, marketing prospects and patent-related issues should be investigated as part of feasibility decisions but are not discussed here.

**Risk assessment for candidate products**

**General concepts**

Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm (12, 13). The evaluation of risk requires identification of a hazard and of the likelihood of its occurrence. An assessment of the degree of risk must also take into account the likelihood of detection of the event prior to the negative outcome. Risk can be lowered through reduction of the impact of the hazard, reduction of the likelihood of occurrence and an increase in the means of early detection and remediation. The risk assessment for candidate products for local manufacture in LMICs thereby involves the evaluation of risk across the spectrum of unit operations and criteria involved in the output of a dosage form. These should be assessed both individually and collectively and their mitigation options evaluated to arrive at a feasibility recommendation. Attributes of the APIs, excipients and the final dosage form have been considered here, specifically as they impact risk to manufacturability. A risk assessment template has been included as an optional tool for systematically documenting the evaluated criteria and their collective recommendations on product candidates for further consideration.

In addition to this document, the availability of and access to information for technical and scientific evaluation and decision-making must also be considered. In accordance with WHO’s guide on *Pharmaceutical development of multisource (generic) pharmaceutical products – points to consider* (8), the availability of supportive documentation including compendial monographs, scientific literature, patents, technical information typically found in the applicant’s open part of the API master file (APIMF), technical information on excipients and prior company knowledge should also be evaluated during a feasibility exercise.

It is assumed throughout that patent and intellectual property considerations have been assessed and allow progression to technical evaluation stages.

**Risk ranking of manufacture of dosage forms (product categories)**

Tran *et al.* (14) have described the development, implementation and results of an expert elicitation survey conducted amongst U.S. FDA experts. Risks associated with the manufacturing processes of a range of medicinal product categories were explored, with

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\(^2\) Defined as countries with a gross national income (GNI) per capita of US$ 1046-US$ 4125 (see: [http://data.worldbank.org/about/country-and-lending-groups](http://data.worldbank.org/about/country-and-lending-groups))
consideration of the manufacturing unit operations required for the product categories. Two broad types of process-related factors were identified, namely:

- factors associated with maintaining process control (process control variables), and
- factors associated with potential vulnerability to product or environmental contamination (contamination variables).

The survey posed the following three questions to capture the experts’ input on three mutually exclusive elements of risk to “loss of control” deemed to be critical:

- To what degree does this unit of operation contribute to variability in quality of the final product?
- How difficult is it to maintain this unit of operation in a state of control?
- If a problem does occur, how reliable are the current detection methods?

With respect to contamination, the following two questions were set to the experts:

- Is this unit of operation more or less vulnerable to contamination from the environment?
- Is this unit of operation more or less vulnerable to contamination from a previous product?

From this work, the ranking outcome of product categories for potential loss of state of control and contamination risks is shown in Table 1.

### Table 1. Risk ranking of product categories by potential loss of control and contamination risk

<table>
<thead>
<tr>
<th>Product category</th>
<th>Risk ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Potential loss of state of control</td>
</tr>
<tr>
<td>Biotech</td>
<td>5</td>
</tr>
<tr>
<td>Liquids, sterile suspension/emulsion</td>
<td>5</td>
</tr>
<tr>
<td>Liquids, sterile solution</td>
<td>5</td>
</tr>
<tr>
<td>Metered dose inhalers, low and high API load*</td>
<td>5</td>
</tr>
<tr>
<td>Powders, low API load</td>
<td>4</td>
</tr>
<tr>
<td>Semisolsids (ointment/cream), low API load</td>
<td>4</td>
</tr>
<tr>
<td>Solid orals, modified release, low API load</td>
<td>4</td>
</tr>
<tr>
<td>Transdermal</td>
<td>4</td>
</tr>
<tr>
<td>Liquids, non-sterile suspension/emulsion</td>
<td>3</td>
</tr>
<tr>
<td>Semisolsids (ointment/cream), high API load</td>
<td>3</td>
</tr>
<tr>
<td>Solid orals, modified release, high API load</td>
<td>3</td>
</tr>
<tr>
<td>Solid orals, immediate release, low API load</td>
<td>3</td>
</tr>
<tr>
<td>Powders, high API load</td>
<td>2</td>
</tr>
<tr>
<td>Solid orals, immediate release, high API load</td>
<td>2</td>
</tr>
<tr>
<td>Liquids, non-sterile solution</td>
<td>1</td>
</tr>
</tbody>
</table>

* Although “high API load” has not been defined in the paper of Tran (14), it is taken for the purpose of this document as the case where the API(s) present at ≥ 5 mg and ≥ 5% of the weight of the dosage unit (The International Pharmacopoeia for mass uniformity).

As risk ranking scores increase, the prospects for manufacture of candidate products in start-up scenarios in LMICs become less favourable. Product categories where the potential loss of state of control has a score of 4 or higher are unlikely candidates for start-up manufacture in LMICs. Therefore products of biotechnology, sterile dosage forms, inhaled products, most dosage forms containing low amounts of API (more potent APIs) and transdermal preparations are relatively unfavourable candidates. Risks associated with manufacture of these dosage forms are discussed below.

In general, feasibility of essential medicines production by start-up manufacturers in LMICs is highest for product categories with lowest possible risk, with consideration of the experience of the manufacturer, availability of qualified human resources and the regulatory capacity of the NMRA. Products falling into the shaded sections in Table 1 are the most attractive for manufacture in LMICs.
Risks to consider for starting materials used in pharmaceutical products

The manufacture of starting materials, such as APIs, are out of scope of this document. However, the attributes of starting materials influence risk to the manufacturing operations or quality, safety and efficacy of the finished pharmaceutical product (FPP). The characteristics of the API, excipients and other ingredients used in manufacture may affect the product feasibility level.

Active pharmaceutical ingredients

The Biopharmaceutics Classification System

In 1995 the American Department of Health and Human Services, U.S. Food and Drug Administration (U.S. FDA) initiated the Biopharmaceutics Classification System (BCS) with the aim of granting biowaivers for scale-up and post-approval changes (15). The BCS was later developed to support the waiving of bioequivalence (BE) studies of certain orally administered generic dosage products by US-FDA (16), by WHO (17, 18) and by EMA (19).

The BCS classifies APIs in four classes according to their solubility in aqueous medium and their intestinal permeability properties as shown in Table 2.

<table>
<thead>
<tr>
<th>Class</th>
<th>Solubility</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>3</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>4</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

Table 2. Classification of APIs according to the BCS

Of particular importance is the WHO definition of high solubility (18):

“An API is considered highly soluble when the highest single therapeutic dose as determined by the relevant regulatory authority, typically defined by the labelling for the innovator product, is soluble in 250 mL or less of aqueous media over the pH range of 1.2–6.8. The pH-solubility profile of the API should be determined at 37 ± 1°C in aqueous media.”

The highest single therapeutic dose may be higher than the highest dose recommended by WHO in the EML. The package leaflet of the comparator (innovator) product can be consulted to establish the highest single therapeutic dose of a particular product.

The BCS also found wide application in pharmaceutics and especially provides an approach to the description of solubility of APIs, related to the dose and not to the classical definition of solubility presented in the pharmacopoeias.

Generally it can be concluded that, taking only the BCS into account, the risk associated with the development of oral dosage forms is lowest for Class 1 and highest for Class 4 (Figure 1).

Figure 1. Risk by biopharmaceutics classification
Correct BCS classification of the API is important. Manufacturers are advised to use reliable information from peer-reviewed literature and regulatory authorities, as well as the General notes on Biopharmaceutics Classification System: (BCS)-based biowaiver applications available on the WHO Prequalification website. The series of Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms published for a number of APIs in the Journal of Pharmaceutical Sciences are useful for reliable BCS classification.

**Solubility**

Solubility of the API is relevant to manufacturability, testing and in vivo performance of a product. Non-sterile solutions (oral or topical) containing an API belonging to BCS Class 1, and to slightly lesser degree Class 3, are the most favourable candidates, followed by immediate-release solid oral dosage forms containing a high dose of a Class 1 API, and to a lesser degree Class 3, to select for development for manufacture in LMICs.

Quality control testing for lot release is aided by API of high aqueous solubility, including content uniformity and dissolution testing.

Solubility data at pH 1.2 (or 0.1 M HCl), pH 4.5 and pH 6.8 can be used to establish whether the API is of BCS high or low solubility across the pH range through reference to literature data. A simple indicator that an API is likely of low solubility across the physiological pH range is if the dissolution medium of the product in pharmacopoeial test methods contains a surfactant.

**Polymorphism and particle size**

Particle size distribution (PSD) and polymorphism are considered critical quality attributes (CQAs) when the API is of low solubility (BCS Class 2 and 4), since it may affect the performance of the final dosage form, such as its dissolution rate and absorption, for example, solid oral dosage forms, oral suspensions and delivery of inhalation products. It may also be important in achieving uniformity of content in low-dose tablets (e.g. 2 mg or less), desired smoothness in ophthalmic preparations and stability of suspensions.

Particle size, polymorphic form and/or crystal habit of an API of any class may affect the manufacturability of a solid dosage form since these may, for instance, affect the flow properties of the blend for compression.

In addition, if the solubility of the Class 2 or 4 API is low across the physiological pH range (1.2 to 6.8), control over particle size distribution of the API becomes highly critical in solid oral dosage forms and oral and injectable suspensions. This is due to the fact that the dissolution medium for these dosage forms containing such API would require the presence of surfactants. It is highly unlikely that the dissolution rate is discriminatory in the presence of surfactants – thus the discriminatory release parameter for the product is actually the particle size distribution (with D50 as a range) of the API contained therein. Though this is more of a development aspect, it must be taken into account that the PSD acceptance criteria should always be set on the results obtained for the API batch used in the manufacture of the FPP batch (for retention of the biobatch CQA). The importance of PSD in product performance, development studies and control is described in WHO’s Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part (20).

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**Hygroscopicity**
Absorption of water by APIs in solid dosage forms introduces quality and stability risks to the product. Water uptake may result in tablet friability and resistance to crushing problems, powder caking and product degradation. Manufacture of a product containing a highly hygroscopic to deliquescent API is at moderate risk, and mitigation measures must include humidity control during any exposure to the manufacturing environment. Protective packaging for tablets and capsules, such as Alu/Alu strips or desiccants in bottle packs, may also be required.

Definition and determination of hygroscopicity can be guided by pharmacopoeial monographs, supplemented by a literature search and/or in-house studies.

**Stability**
Stability is regarded as a relative term. API stability considerations are provided as a guide for risk assessment. Where available scientific literature describes the API as very stable, the risk of selecting the candidate product containing this API is lowered. If a retest period of three or more years has been allocated for storage at “not above 30°C” or “room temperature” without special precautions, the indication is that no significant changes are seen during these storage conditions in the specified packaging and stability risk is regarded as low. If a shelf life rather than a retest period is allocated, the API may not be considered very stable under the storage conditions in the API packaging, especially when storage under nitrogen is recommended. Stability data in solution or open dish experiments offer additional guidance. If an API should be stored at refrigerator conditions, the risk should be considered high, particularly where implementation of refrigerated facilities is problematic. Pharmacopoeias, standard works, public assessment reports (PARs) and literature should be consulted.

**Supply and procurement**
Readily available APIs with no history of supply shortage present the lowest risk of continued availability for local manufacture. APIs used in well-established multisource products are the most favourable candidates (8). Compounds not yet genericized are not favourable unless the start-up manufacturing model is actively supported by the innovator company.

Since manufacturing development and quality control risks are most effectively mitigated through product knowledge, candidate products with APIs found in standard pharmacopoeial monographs increase favourability. Robustness of candidate selection is increased where a Certificate of suitability of Monographs of the European Pharmacopoeia (CEP) is available. A valid CEP identifies that the API meets the European Pharmacopoeia standard. A list of valid CEPs may be found on the European Directorate for the Quality of Medicines & HealthCare (EDQM) website.

Sourcing of an API of assured quality decreases the technical and resource burden of supplier qualification. Therefore APIs that have been prequalified by WHO reduce risk and burden for dosage form manufacturers, since the API and the API manufacturer’s site and GMP system have been evaluated (21). The WHO Prequalification Team – Medicines (WHO-PQTm) website should be consulted for the list of prequalified APIs; the list may include APIs that are not described in pharmacopoeias, which may be attractive for manufacturers. The list is continuously updated.

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4 EDMQ Certification online database: https://extranet.edqm.eu/publications/recherches_CEP.shtml
5 http://apps.who.int/prequal
Storage and transport
The ability to store, transport and receive shipments of the API in a manner that maintains the quality of the material must be considered. APIs with stability precautions (see above) such as heat-labile and/or highly hygroscopic materials require robust transportation routes and warehousing facilities. Selection of such candidates should not be undertaken unless these are available or can be put into place as an element of the start-up planning.

Active pharmaceutical ingredients of biological origin
The manufacture of APIs is out of scope of this document. However, it is noted that the EML includes biologically derived products, namely vaccines, which are manufactured in a number of countries falling within the definition of an LMIC. Final dosage form manufacture with biological API requires specific considerations and precautions arising from the nature of these products and their processes (22). Biological APIs are often highly labile and vulnerable to loss of quality, and have the highest contamination risk (see Table 1). Manufacture of products using this class of APIs is of highest risk and of lowest likelihood of feasibility in a start-up scenario.

Excipients and other inactive pharmaceutical ingredients
Evaluation of excipients for suitability in dosage forms in a manufacturing plan follows similar technological principles as selection of the API. The availability of quality sources of the inactive pharmaceutical ingredients and stability of these through transport, storage and product manufacturing operations must be evaluated in parallel with the evaluation of APIs. The fewer the required excipients the lower the risk to reliable procurement of quality materials for production. Excipient selection in the context of formulation considerations is further discussed below. Novel excipients should be avoided as they increase risk to reliable supply, and significantly increase the burden of evidence of pharmaceutical development, and clinical evidence of their quality control, safety and impact to bioavailability (BA) and bioequivalence. Non-pharmacopoeial excipients are not recommended since the regulatory authority may request an APIMF (Drug master file, DMF) and safety data for such excipients.

In addition, in some manufacturing procedures such as wet-blend granulations for tablet manufacture, inactive ingredients such as water and organic solvents may be required in the manufacturing process that are not present in the final dosage form. These inactive ingredients must be controlled in the same manner as excipients, complying with compendial requirements.

Risks to consider for final dosage form
Dosage format manufacturing considerations
For successful implementation of pharmaceutical manufacturing capability in LMICs the complexity of the final dosage form has a significant impact. Risk to successful implementation increases with increasing complexity of manufacture. Therefore, non-sterile liquid dosage forms where the API has high aqueous solubility, and the where capabilities for measuring and blending are available, are of highest feasibility. Incompletely soluble ingredients in suspensions and emulsions require capabilities for emulsification, heating and cooling and increase the requirement for controls for achieving homogeneity and content uniformity.
Solid oral dosage form manufacture is, in most cases, more complex than the manufacture of non-sterile solutions. These may be powders for solution, capsules and tablets. Along with measuring, all require blending capabilities. Capsule and tablet formulation may require a granulation phase, which may be a dry granulation process or a “wet” granulation process using water or an organic solvent. The latter is further dried, and blends are often milled to achieve critical particle size attributes required for flow in the capsule filling or tablet compression stage, as well as to achieve appropriate dissolution, bioavailability and bioequivalence to a reference product. Functional film coating and modified release formulations increase the technological complexity further.

The greater the number and complexity of unit operations, the higher is the requirement for manufacturing facility capabilities, depth and diversity of technical expertise, and for measures to maintain process control and mitigate contamination risk. The risk ranking of dosage forms in Table 1 reflects these concepts.

Fixed-dose combination products (FDCs), for the purpose of this document, are those where two or more APIs are co-formulated in the same dosage unit, for example in tablets or solution. Generally FDCs are discouraged when considering products for start-up manufacture in LMICs. This is due not only to possible increased manufacturing constraints, but also to specific challenges in specification limits, content uniformity and tests for related substances, in particular degradation products. When the APIs are known to be incompatible, e.g. rifampicin and isoniazid, FDCs should not be considered. Exceptions may be considered when the APIs are of Class 1 or 3, when a monograph in The International Pharmacopoeiae, British Pharmacopoeia, United States Pharmacopeia or other official NMRA pharmacopoeia is available for the particular FDC and when a comparator FDC exists. If an FDC is considered, a similar feasibility exercise as for mono-component final dosage forms should be followed.

For some dosage forms, such as metered dose inhalers and transdermal patches, the primary packaging is critical to dose delivery. The technological capability requirements, like those of sterile solutions and sterile injectable product manufacture, are unlikely to be compatible with a start-up manufacturing project unless supported by critical commitment from a parent pharmaceutical enterprise with experience.

**Formulation**

The complexity of the formulation of the final product usually aligns with the technological capability requirements for finished dosage form (FDF) manufacture. It follows that formulations with fewer ingredients and less complex ingredients are likely to be more favourable as candidates for start-up manufacture in LMICs. They usually require fewer unit operations of manufacture to validate and control, pose lower risks for procurement of ingredients, and may have less technologically demanding product testing requirements. Examples of formulations with added complexity are fixed-dose combination products and functionally coated or modified release solid oral dosage forms, described above. Liquid non-sterile solutions and immediate-release solid oral dosage forms are the most feasible candidates (Table 1).

Manufacturing feasibility of multisource FPP is increased when there is higher access to information on the comparator product. Information about the comparator product composition helps to inform verification of bioequivalence and of the feasibility of seeking biowaivers, to provide preliminary expectations of stability and shelf life, and to inform the selection of appropriate packaging.
Knowledge of the comparator’s qualitative composition reduces the development burden of API–excipient compatibility studies. Where quantitative information about the composition of the comparator is known and quantitative information is available on excipients that may have an effect on bioavailability, development risk is further reduced. If the comparator is available at the same strength as the candidate product, required development capabilities and risks are further reduced.

**Bioequivalence and dissolution**

Class 1 APIs and Class 3 APIs with BCS high solubility are most readily bioavailable. Where the candidate product is a multisource (generic) product, bioequivalence studies versus the comparator may be waived for immediate release solid oral dosage forms containing a Class 1 API under certain conditions and Class 3 API under more stringent conditions (18) (also see the General notes on Biopharmaceutics Classification System: (BCS)-based biowaiver applications on the WHO-PQTm website). Therefore, where supported by technical sources and appropriate comparative dissolution profiles, these dosage forms have a lower burden of development data as they potentially omit clinical studies.

Where the dissolution profile in the laboratory test environment has been shown to be similar for the multisource and the comparator product the chance for a positive bioequivalent study outcome is enhanced. Thus targeting of the comparator product dissolution profile is an essential part of the development and can be useful in supporting the initial marketing authorization as well as life cycle manufacturing changes (20).

Compounds known from scientific data sources to have bio-inequivalence problems should be considered unfavourable candidates in start-up manufacture.

**Container closure and primary packaging**

In general, for non-sterile liquid products and solid oral products, pharmacopoeial grade glass or non-reactive polymer bottles are the simplest options for primary packaging. Products requiring specialized primary containers to maintain product integrity throughout shelf life add complexity and reduce feasibility. Where the primary packaging is responsible for accurate dosing and/or requires increased filling and packaging technology (aseptic filling, inhalers and patches) candidate products are unlikely to be compatible with a start-up manufacturing situation.

Wherever possible the primary packaging of a multisource product should follow that of the comparator. If the manufacturer cannot perform the packaging in alignment with the comparator or other multisource products, the burden of packaging development and stability data increases.

**Stability**

Stability of the FPP must be evaluated in the assessment of candidate products. Robust stability of the API and excipients, together with stability of the product, are the criteria for the most favourable candidates. Where the qualitative composition of the comparator product is known this can be used to inform stability of a candidate formulation. The storage instructions and assigned shelf life of the comparator or other multisource products can be used as a measure of final product stability in the proposed packaging. Evaluation should include the climatic zone of the proposed site of manufacture, and facility capabilities should adequately control the manufacturing environment, including temperature and relative humidity. If storage instructions of comparable products are “store in refrigerator” or
lower temperature, the control of temperature throughout the manufacturing unit operations should be expected to require similar controls. The risk of loss of product quality due to loss of temperature control makes this class of product significantly less favourable as a candidate.

Storage and transport
Essential medicines, whether imported or locally manufactured, must be transported and stored in the country of distribution and use. The burden of evidence for product quality and stability throughout storage and transport is the responsibility of the manufacturer. This includes generation of data for initial market authorization, as well as re-establishment as needed during manufacturing life cycle changes. Product candidates requiring specialized storage and transport will increase resource and technological demands on the manufacturer, and the feasibility of ongoing life cycle support of such candidates must be considered in the overall selection exercise. It is quite important for the manufacturer to take into account the climatic conditions prevailing in the countries targeted for commercialisation. It is suggested that requirement for Zone IVb storage conditions be assessed when considering the development plan for long term studies.

In-process quality control requirements
All manufacturing unit operations must be executed in a state of control to mitigate quality failures during production and their consequent impact in terms of loss of production batches or, in the case of poorly detected failure, impact to safety and efficacy. It follows then, that the more unit operations required for FDF production, and the more technologically demanding their control within required parameters, the higher the risk of quality failure (Table 1). Start-up manufacturing projects are at lowest risk for product candidates requiring the fewest and least complex manufacturing operations, for example measuring, solubilising and filling for liquid non-sterile solutions. As complexity increases through operations such as emulsion, granulation, drying, milling, tablet compression and film coating, each step must be controlled for such factors as time, temperature, mixing speed and completeness to target (dryness, particle size, homogeneity, coating coverage). Manual control of certain operations reduces the technological dependence of the operation but has the potential to increase variability and may not be acceptable for risk reasons by some regulatory authorities.

In selecting product candidates the number and complexity of manufacturing operations, whether there are options for manual or automated process controls, the technological and human resource expertise and training available to maintain them, and the hazards and detectability of errors need to be considered.

Testing considerations
The capabilities for product testing should be considered both for in-process control testing and finished product testing, the latter including release and stability testing. As the complexity of the product category and dosage form increases, so may the complexity of analytical testing. Analytical testing requiring the highest technologies of test instrumentation, such as mass spectrometry, or unique and difficult-to-source materials, such as specialized chromatographic reagents and columns, may not be suited to start-up manufacturing scenarios. Where pharmacopoeial monographs for the API and the excipients are available testing is facilitated and the risk of analytical errors or lack of detection of quality failures is reduced.
**Facilities considerations**

Feasibility assessment for any pharmaceutical manufacturing endeavour must include assurance of the ability to construct fit-for-purpose buildings, procure and maintain the required equipment and have access to reliable utilities. Licensed products should be manufactured by licenced manufacturers whose GMP activities are regularly inspected by competent authorities (23). Manufacturing facilities must be capable of executing operations in a state of GMP compliance. Initial establishment and continued maintenance of manufacturing facilities are more demanding where there are requirements for specialized facility capabilities and environmental controls. Some level of climate control in the manufacturing environment will be necessary in all GMP-compliant facilities and may include room temperature and relative humidity control. However, reduction in risk of cross-contamination of products and materials may require varying degrees of segregation of manufacturing suites, dust control, air pressure cascades, HEPA filtration, gowning and showering requirements. Risk of cross-contamination and therefore risk mitigation is of highest consideration for product manufactured with cytotoxic or highly potent actives, steroids, hormones or infectious agents. In addition, facility capabilities may be a critical control factor for product quality, for example, refrigeration of cold chain products. Facilities considerations therefore mirror manufacturing considerations, and must be integral to the product candidate identification process. Product categories in the shaded sections of Table 1 are the most favourable candidates.

**Clinical risk considerations**

**Potency and therapeutic index**

Variability in product manufacture and control, for example in homogeneity and content uniformity, poses the greatest risk to clinical safety and efficacy where the API is highly potent or has a very narrow therapeutic index. Guidance on potency and therapeutic index should be verified in the scientific literature as part of the evaluation exercise. Examples of APIs with a narrow therapeutic index include chloramphenicol, lithium, phenytoin, and warfarin (17). Therefore the same units of operation performed to manufacture FDFs with less potent actives or those with wider therapeutic index should be considered of higher risk when the API is a more potent compound or one with a narrow therapeutic index. For local manufacture in a start-up situation product categories that are higher in API/lower in potency (Table 1) are more favourable choices until manufacturing experience in the relevant unit operations is well established.

**Target populations**

Where a product is intended for an identified subset of patients, consideration should be given to whether the intended population differs in its metabolism of the product, and to the pharmacokinetic profile of the product in this population. Examples are where pharmacokinetics and bioavailability are altered by age (in paediatric or geriatric populations), and hepatic or renal impairment. The potential impact on risk of any manufacturing operations, such as processing parameters known to impact bioavailability or bioequivalence, should then be considered. Risk is lowered where comparators provide clinical experience in special populations in their labelling, the qualitative composition of the comparator is known and the manufacturing processes are relatively low in complexity.
**Genotoxicity**

Some APIs are manufactured by synthesis pathways in which genotoxic raw materials are used or genotoxic by-products may form. If the API is a mesilate salt, or if primary information sources such as the API monograph or public assessment reports (PARs) include a test for a potential genotoxic or mutagenic impurity, product candidates containing the API are less favourable. The API monographs of *The International Pharmacopoeia* and the European Pharmacopoeia can be consulted for possibility of tests for mesilates (aryl or alkyl sulfonates) or other potential genotoxic (mutagenic) impurities. Similarly PARs such as the WHOPARs should be consulted. Further references are available (24, 25, 26, 27, 28).

Genotoxic impurities are controlled at parts-per-million levels according to EMA (29) and require sophisticated laboratory analytical capabilities such as gas chromatography–mass spectrometry (GC-MS). When considering the feasibility of product candidates with the potential to contain genotoxic impurities appropriate testing capabilities must be established. Risk can be reduced if the API with potential genotoxic impurity is obtained from a manufacturer with a CEP or if it is WHO-prequalified. The potential API manufacturer(s) should also be qualified in this respect and the open part of APIMF/DMF well evaluated.

**Taste**

Some APIs may have a taste that requires masking, for example zinc sulfate. This may be done physically, through manufacturing operations such as film coating of tablets, or chemically through the formulation in the case of dispersible, soluble, chewable or crushable tablets and powders. Film coating applies additional manufacturing operations as described under “Dosage format manufacturing considerations” above. Masking agents in a formulation may affect the bioavailability of the API, which should be verified in development work and when considering bioequivalence to comparator products.

The WHO publication *Production of Zinc Tablets and Zinc Oral Solutions: Guidelines for Program Managers and Pharmaceutical Manufacturers* (30) provides general information regarding the design of the acceptability study in Chapter 5 and Annex 8. Such studies are required by WHO-PQTm in applications for prequalification of invited zinc sulfate dispersible tablets and oral solution. The WHO-PQTm website can furthermore be consulted with respect to a draft protocol for acceptability studies, acceptable taste masking excipients and general requirements regarding zinc sulfate and dosage forms.

**Human resource points to consider**

Considerations of the complexity of the unit operations of manufacture, process controls and finished product testing throughout the product candidate evaluation process for manufacture in LMICs have been discussed. The assessment of manufacturing feasibility and the identification of candidates that can be successfully produced must include an assessment of not only the requirements for the physical facilities and equipment and their related technologies, but also the human resources needed to consistently operate within a state of control. Establishment of a manufacturing facility in countries with little previous pharmaceutical manufacturing presence will require operational, analytical and information technology, GMP and regulatory training commensurate with the degree of complexity of the candidate product manufacture.
Capabilities of the NMRA to regulate local pharmaceutical manufacturing and licensing

Any exercise in which the feasibility of local manufacture of a medicinal product is assessed must consider not only the capabilities of the manufacturer, but also the capacity of the local NMRA to effectively assess the dossiers for product registration, to establish GMP regulations and conduct inspections, and to regulate life cycle variations. Product candidates for manufacture must also be considered in the context of the functionality and maturity of the NMRA. Effective and timely access to locally manufactured medicines is dependent on regulatory capacity both in terms of total resources and expertise. A product that is not procured via import, or produced locally and not exported, may rely for its registration and oversight entirely upon the NMRA of the country in which it is produced. Therefore, the capacity of the NMRA should be included as a component of the local manufacturing feasibility assessment, and wherever possible an open dialogue between the potential manufacturer and the NMRA should be undertaken to ensure clarity of requirements, expectations, capabilities and timelines.

Conclusion

Assessment of essential medicines product candidates for local manufacturing in low LMICs is a multifactorial undertaking. The evaluation must consider the diseases to be targeted, costs, capacity, skills, technology requirements and intellectual property rights, among the assessment criteria, in order to determine what may successfully be produced. This document focuses on an assessment of potential product candidates from the perspective of the required manufacturing technology, in conjunction with the risks associated with the product itself, to help identify products more likely to be considered for manufacture in LMICs with limited pharmaceutical manufacturing capability and experience.

Attributes of the APIs, excipients and the final dosage form have been considered, specifically as they impact risk to manufacturability, including packaging, testing and facility requirements. The risks to product quality, specifically for manufacturers with limited experience, are presented to provide a rationale for identifying candidates for further evaluation. A tool for systematically reviewing the attributes is provided, accompanied by a scoring schema for differentiating likely and unlikely candidates. The attributes are not intended to be exhaustive of all possible product and material characteristics, but to provide the range of criteria that can be used to review the WHO EML/EMLc.

The completion of any risk assessment exercise depends upon the sourcing of available and accurate supportive technical and scientific information. This document should therefore be used in conjunction with the cited references and other scientific source documents to populate the evaluation template or similar tool.
Risk assessment template for candidate products

**Primary information on candidate product**

<table>
<thead>
<tr>
<th>Candidate product (INN, dosage form, strength)</th>
<th>Listed in EML/EMLc?</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCS classification of API (provide supportive reference)</td>
<td></td>
</tr>
<tr>
<td>Relative manufacture risk ranking (Table 1)</td>
<td></td>
</tr>
</tbody>
</table>

Where risk ranking is ≥ 4, is the manufacturer and operation strongly supported by an experienced partner or parent entity? (Yes/No) If no, provide a rationale for continued assessment.

Proceed to comparator* assessment table (Yes/No)

* The WHO Expert Committee on Specifications for Pharmaceutical Preparations published in 2002 a list of international comparator products as part of the Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products (31). The general principles included in this guidance were subsequently revised (32). The list itself is currently undergoing a major revision.

**Information on comparator (innovator) product (NMRA, ICH or WHO-PQTm)**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator product available?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparator product name (brand/dosage form/strength)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indicate all available strengths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country/region of comparator product information</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qualitative composition, if available (only core for coated tablets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>List excipients that may affect bioavailability (BA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantities provided of excipients that may affect BA? (Yes/No. If Yes, provide quantities)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If tablets, are they coated?</td>
<td></td>
<td></td>
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<tr>
<td>What is the function of the coating?</td>
<td></td>
<td></td>
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<tr>
<td>Primary packaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Storage conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shelf life, if available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other comments on comparator of importance for selection process, if any</td>
<td></td>
<td></td>
</tr>
<tr>
<td>May a biowaiver be possible for candidate product? (If yes, clarify briefly)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Risk assessment for candidate product**  
Scores from 1 (low risk) to 4 (high risk) and 5 (not recommended)

<table>
<thead>
<tr>
<th>Item No.</th>
<th>Aspects to consider</th>
<th>Dosage form affected</th>
<th>Risk assessment guide</th>
<th>Score 1 to 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active pharmaceutical ingredient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **A1** Therapeutic index | All | If API is of narrow therapeutic index (NTI), score = 5  
If API is potent, score = 3 (below 5 mg per dose)  
If API is highly potent, score = 5 (below 1 mg per dose)  
Otherwise score = 1 | | |
| **A2** Genotoxicity | All | If the API is a mesilate salt, or if primary sources (e.g. API monograph and PARs) include a test for a potential genotoxic impurity, score = 5.  
If the API with potential genotoxic impurity will be obtained from a manufacturer with CEP or API-PQ, score = 1 (The correct certification procedures should be followed).  
Otherwise score = 1 | | |
| **A3** Monograph/specifications | All | If the API has a pharmacopoeial monograph, score = 1  
If the API is prequalified and/or has a CEP, score = 1  
Otherwise score = 4 | | |
| **A4** Solubility | Solid dosage forms | If the API is of BCS Class 2/4 and the solubility is low across the physiological pH range (from pH 1.2 to pH 6.8), score = 5  
Otherwise for an API of BCS Class 2/4, score = 3  
If the API is of BCS Class 1 or 3, score = 1 | | |
| **A5** Hygroscopicity | Solid dosage forms | Highly hygroscopic to deliquescent, score = 3, hygroscopic score = 2, slightly or none score = 1 | | |
| **A6** Stability, storage and transport | All | If API should be stored at refrigerator conditions, score = 4 and if no refrigerator facilities are available, score = 5. If known from literature or data to be very stable, score = 1.  
If a shelf life (not retest period) is allocated, score = 3  
If retest period of ≥ 3 years at "room temperature" is allocated without special precautions, score = 1 | | |

*Continued*
<table>
<thead>
<tr>
<th>Item No.</th>
<th>Aspects to consider</th>
<th>Dosage form affected</th>
<th>Risk assessment guide</th>
<th>Score 1 to 5</th>
</tr>
</thead>
</table>
| A7      | Bioequivalence and dissolution              | All                  | If the API(s) is known for bio-inequivalence problems, score = 5  
|         |                                             |                      | Otherwise score = 0 |              |
| A8      | Biologics                                   | Injectable           | If the active ingredient is a biologic, score = 5                 |              |
| A9      | Supply and procurement                      | All                  | If the API is well-established and is readily available with no history of supply issues, score = 1  
|         |                                             |                      | If the API is prequalified and/or has a CEP, score = 1           |              |
|         |                                             |                      | If the API is not well-established and there is no prior agreement on sourcing, score = 5 |              |
| E1      | Monograph/specifications                    | All                  | If the excipients have pharmacopoeial monographs, score = 1       |              |
|         |                                             |                      | Otherwise, score = 5                                             |              |
| E2      | Stability, storage and transport            | All                  | If excipients/raw materials should be stored at refrigerator conditions, score = 4 and if no refrigerator facilities are available, score = 5.  
|         |                                             |                      | If known from literature or data to be very stable, score = 1.   |              |
|         |                                             |                      | If a shelf life (not retest period) is allocated, score = 3      |              |
|         |                                             |                      | If retest period of ≥ 3 years at “room temperature” is allocated without special precautions, score = 1 |              |
| E3      | Supply and procurement                      | All                  | If the material is readily available with no history of supply issues, score = 1  
|         |                                             |                      | If the material is not readily sourced, score = 3                |              |

Excipients, including those that are removed during manufacture

Continued
<table>
<thead>
<tr>
<th>Item No.</th>
<th>Aspects to consider</th>
<th>Dosage form affected</th>
<th>Risk assessment guide</th>
<th>Score 1 to 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>From Table 1:</td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>Dosage format</td>
<td>All</td>
<td>If the risk ranking for loss of control is 1 or 2, score = 1</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>If the risk ranking for loss of control is 3, score = 3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>If the dosage format is complex and risk ranking for loss of control ≥ 4, score = 5</td>
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<tr>
<td></td>
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<td></td>
<td>If the product is a fixed-dose combination and the APIs are all Class 1 or 3, score = 3</td>
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<tr>
<td></td>
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<td></td>
<td>If the product is a fixed-dose combination and one or more APIs are not Class 1 or 3, score = 5</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>If the product is a fixed-dose combination and the actives are considered incompatible, score = 5</td>
<td></td>
</tr>
<tr>
<td>F2</td>
<td>Composition</td>
<td>All</td>
<td>If the quantitative composition of the comparator is known, score = 1</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>If the qualitative composition of the comparator is known, score = 2</td>
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<td></td>
<td></td>
<td></td>
<td>Otherwise score = 5</td>
<td></td>
</tr>
<tr>
<td>F3</td>
<td>Monograph/specifications</td>
<td>All</td>
<td>If a pharmacopoeial monograph for the product is available, score = 1</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td>If pharmacopoeial specifications require a surfactant in the dissolution medium, score = 5</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Otherwise score = 5</td>
<td></td>
</tr>
<tr>
<td>F4</td>
<td>Primary packaging</td>
<td>All</td>
<td>If the primary packaging is critical to accurate dosing score = 5 (e.g. metered dose inhalers)</td>
<td></td>
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<td></td>
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<td></td>
<td>If the product is sterile, score = 5</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>If the manufacturer cannot do the packaging as required by comparator or other generic products, score = 3, otherwise score = 1.</td>
<td></td>
</tr>
</tbody>
</table>
### Item No. | Aspects to consider | Dosage form affected | Risk assessment guide | Score 1 to 5
---|---|---|---|---
F5 | Stability, storage and transport | All | If the storage instructions of the comparator or other multisource products, e.g. WHO-prequalified products, can be used to predict stability and product is stable without specialized conditions, score = 1
If a PAR (e.g. WHOPAR, EPAR) is available and it indicates that the product is relatively stable, score = 1
If the product requires protective packaging, score = 3 (The final product must be stable enough to be stored under the conditions required by the NMRA, Zone II, III, IVa or IVb).
If storage instruction is “store in refrigerator” or lower temperature, score = 4 | | |
F6 | Target population | Oral, rectal | If the formulation is predicted to have altered bioavailability in target subpopulations and the manufacture is at risk of introducing bio-inequivalence, score = 5
Otherwise score = 1 | | |
F7 | Taste | Dispersible / soluble / chewable / crushable tablet & powders for solution & solution | If taste requires masking, other than coating, the masking agent(s) may affect bioequivalence and the masking agent(s) is not quantitatively listed in the comparator’s product information, score= 4
If the masking agents are quantitatively listed in the comparator’s product information and/or qualified by WHO-PQTm, score = 1
Otherwise score = 1 | | |

### Outcome of the risk assessment exercise

<table>
<thead>
<tr>
<th>Candidate product (INN, dosage form, strength):</th>
<th>Answer</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any aspect scoring 5 (not recommended)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any one or more scoring 4 or more (high risk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any two or more scoring 3 or more (high risk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One scoring 3, rest 2 or below (medium risk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All scoring 2 or below (low risk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candidate for further development, based on a low risk assessment (Yes/No)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
References


Safety of medicines

The WHO Collaborating Centre for International Drug Monitoring

Detecting and addressing medicines-related problems is critically important for patient safety. As the manufacture and supply of medicines becomes more globalized, so too should the approaches to monitoring the safety of vaccines and medicines. WHO, through its Programme for International Drug Monitoring, works with the Uppsala Monitoring Centre (UMC) to maintain the world’s single global repository of data on adverse drug reactions and to promote good pharmacovigilance practices in Member States.

Background
Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (1). Although all medicines are rigorously tested in clinical safety and efficacy trials before they are made publicly available, most of the safety data on medicines only becomes known once the products are on the market. Continued monitoring in real world settings, where medicines are used in conjunction with other products, among different patient populations and in patients with multiple illnesses, is therefore critically important.

WHO promotes medicines safety in Member States in several ways. The organization develops normative guidance with a focus on low- and middle-income countries, supports countries in implementing best pharmacovigilance practices, and communicates regulatory decisions and safety signals for medicinal products at a global level.

WHO Programme for International Drug Monitoring
An important part of WHO’s medicines safety work is the Programme for International Drug Monitoring (PIDM). The WHO PIDM members submit Individual Case Safety Reports (ICSRs) into a global database.

The ICSRs submitted by member countries are managed by the WHO Collaborating Centre for International Drug Monitoring, known as the Uppsala Monitoring Centre (UMC)1. With over one hundred staff and consultants, UMC carries out a wide range of activities to support and promote patient safety through effective global pharmacovigilance practice. The centre maintains relationships with hundreds of individuals, institutions, professional societies, research units, government

1 www.who-umc.org

This article is based on the Annual Report 2015 of the Uppsala Monitoring Centre (UMC) (2). We thank Paula Alvarado and Lembit Rägo for their useful input.
departments and commercial operations. UMC receives a sustained flow of guidance through the WHO Advisory Committee on the Safety of Medicinal Products (ACSoMP) and WHO-appointed UMC Board members.

**A global database**

The core repository of ICSRs submitted globally is the VigiBase™ database, which is developed and maintained by the UMC on behalf of WHO.

In December 2015 there were 122 WHO PIDM member countries and a cumulative total of over 11 million ICSRs submitted to VigiBase (Figure 1), including more than one million reports from low- and middle-income countries. From 2017, VigiBase will receive ICSRs transferred by the European Medicines Agency (EMA) on a daily basis (see also page 57).

UMC has developed a range of data management and analysis tools in support of VigiBase, notably the web-based ICSR management system VigiFlow™ – provided free of charge to WHO PIDM members as a limited-access version enabling electronic ICSRs reporting – and the search and analysis tool VigiLyze™.

In 2015, aggregated safety data from VigiBase became accessible to the public through the launch of VigiAccess™.

**Research**

With VigiBase as the sole global database of safety information, the detection and dissemination of signals of suspected drug safety concerns is a major focus of UMC’s work. A total of 42 signals were detected, assessed and published in 2015.

Identifying safety signals is rather like finding needles in haystacks. The UMC’s research team is continuously seeking new and better ways of recognizing medicinal problems early in order to protect patients. Some examples include:

- detecting syndromes, when more than one ADR is reported and there is a need to group reports with similar ADR profiles;
- finding risks in specific populations (paediatrics, vaccines, geographical regions);
- highlighting case series with sufficient information for assessment;
- detecting signals in electronic health records;

In 2015, aggregated safety data from VigiBase became accessible to the public through the launch of VigiAccess™.

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2 www.vigiaccess.org
• developing software to analyze free-text narratives in case reports;
• detecting substandard drugs; and
• exploring the potential of social media as a source of patient risk information. Members of the UMC’s research team contribute to professional meetings and research conferences and have won international awards for their work.

UMC also contributes to external collaborative projects. Examples include the PROTECT project aiming to strengthen the benefit-risk monitoring of medicines in Europe by developing and validating new signal detection methods, the SALUS project aiming to develop tools and protocols for mining and analyzing real-time patient data from heterogeneous electronic health records, and WEB-RADR, which aims to leverage mobile-phone reporting and find ways to analyze social media for pharmacovigilance purposes.

In 2009–2013 UMC coordinated the Monitoring Medicines project, a multi-regional pharmacovigilance and public health effort funded by the European Commission (3). This project was developed by WHO and brought together diverse parties to develop methods, tools and guidelines for pharmacovigilance and resulted in significant synergies. Its outputs illustrate how pharmacovigilance activities can serve to detect, assess, understand and prevent not only adverse reactions to medicines, but also threats to patient safety caused by other drug-related problems such as product quality deficiencies or inappropriate use of medicines (Table 1).

Table 1. The Monitoring Medicines project: addressing medicines-related safety issues

<table>
<thead>
<tr>
<th>Stated objectives</th>
<th>Outputs</th>
</tr>
</thead>
</table>
| 1. Support and strengthen consumer reporting of suspected adverse drug reactions (ADRs) | WHO handbook (4)  
Online reporting system (used in six pilot countries, offered free of charge to all VigiFlow users) |
| 2. Expand the role and scope of national pharmacovigilance centres to identify, analyse and prevent medication errors | WHO handbook (5) |
| 3. Promote better and broader use of existing pharmacovigilance data for patient safety | Methodology for detecting drug dependence in spontaneous adverse drug reaction databases (6)  
Methodology for detecting substandard or counterfeit medicines (7) |
| 4. Develop additional pharmacovigilance methods to complement data from spontaneous reporting systems | Publication on WHO strategy for collecting safety data in public health programmes (8)  
Cohort event monitoring (CEM)  
Web-based data management tool CemFlow (used in Belarus, Kenya, Nigeria, Tanzania and Zimbabwe)  
Targeted spontaneous reporting (TSR)  
WHO handbook on pharmacovigilance of medicines used for tuberculosis (9)  
Clinical use of pharmacovigilance data  
Web-based database and risk assessment tool in antiretroviral therapy, available at www.hivpv.org |

Source: Adapted from: (3).
Terminology and coding tools

The data collected in VigiBase are also the source of the content for the WHODrug™ Dictionary portfolio. This UMC resource aims at optimizing the global analysis and reporting of medical product information during the whole life cycle of a drug. WHODrug is mandated in Japan and recommended in the United States for concomitant medications in clinical trials. It is regularly updated with new releases and components to support its use in specific contexts. The 2015 releases include an Enhanced version produced in collaboration with IMS Health, the Cross Reference Tool Japan and the Cross Reference ATC 5.

A mapping bridge has been developed between the WHO Adverse Reaction Terminology (WHO-ART) and MedDRA, the standard terminology of the International Council for Harmonization (ICH). For the future UMC is seeking to collaborate with ICH towards one global terminology solution for both regulatory and pharmacovigilance purposes.

Support activities

Training

UMC carries out training activities in member countries on a wide range of topics including signal detection, the use of data management tools, communications skills and safety reporting processes. Its platform of partners includes the WHO Collaborating Centres in Ghana, Morocco and the Netherlands, the International Society of Pharmacovigilance (ISoP), Jagadguru Sri Shivarathreeswara (JSS) University in Mysore, India, and the Asia-Pacific Economic Cooperation (APEC) among others.

In 2015 UMC organized or participated in pharmacovigilance training courses in Asia, Africa, South America and Europe. Two major events were the 17th annual pharmacovigilance training course held in Uppsala with participants from 28 countries, and the first Asia-Pacific Pharmacovigilance training course in Mysore, India, organized in collaboration with JSS University.

In addition, UMS held webinars on a range of topics in five languages and launched a YouTube channel providing access to over 150 training sessions.

Advocacy

In 2015 UMC launched its first public campaign, Take&Tell™, encouraging patients to tell their health professionals about adverse effects. This innovative and unique campaign raised much interest around the world and was taken on board by a number of national pharmacovigilance centres and other major organizations. It thus achieved its aims to raise global awareness of the importance of pharmacovigilance and to change the way people view the process of taking medicines.

Technical support

UMC provides individual technical support in response to hundreds of – often complex – enquiries and search requests every year. More than 170 search requests from external and internal stakeholders were received in 2015.

Information base

The UMC regularly produces a range of guidelines, manuals and support materials on specific topics such as adverse drug reaction (ADR) reporting forms and data management tools, and makes them accessible online.

3 www.takeandtell.org/
available in the Publications section of its web site. Its quarterly newsletter “Uppsala reports” celebrated its 70th edition in July 2015. UMC also maintains a collection of links to resources available elsewhere, such as pharmacovigilance guidelines produced by member countries and the websites of their regulatory authorities.

Conclusion
The steady growth of membership in WHO PIDM, the high attendance at UMC training events, the increasing uptake of its core tools and the improved quality of reporting by a number of members show that the Programme is reaching a wider audience of patients and health professionals. Many low- and middle-income countries have become active contributors to the WHO PIDM. And at the 2015 annual meeting of WHO PIDM member countries, India proposed to make its Pharmacopoeia Commission the first WHO collaborating centre for pharmacovigilance in the region - a promising development, particularly as many low-cost generic medicines supplied internationally originate in India.

Safer medicines, safer use of medicines and safer patients are high priorities for the world. The results achieved under the WHO PIDM are difficult to quantify, but clearly they have contributed to enhancing pharmacovigilance practices and building a global safety culture. If this work is kept up, it can bring the world closer to UMC’s vision of a place where where all patients and health professionals make wise therapeutic decisions in their use of medicines.

References
Look-alike sound-alike drug name confusion: trastuzumab emtansine

Look-alike sound-alike drug names may be responsible for as many as one in four error reports received by surveillance programs. Not only brand names but also International Nonproprietary Names (INNs) may be subject to look-alike sound-alike confusion, including those for complex products manufactured with new technologies. This article looks at reports of confusion between trastuzumab and trastuzumab emtansine, action taken, and possible future measures that could mitigate the risk of confusion and protect patient safety.

Introduction

Drug name confusion has been well documented in recent years as a contributing factor to the burden of health care-related harm to patients around the world. In particular, look-alike sound-alike drug names have been identified as a significant risk for the occurrence of medication errors. Some estimates suggest that look-alike sound-alike name confusion is responsible for as many as one quarter of error reports received by surveillance programs such as the Institute for Safe Medication Practices (ISMP) Medication Error Reporting Program in the United States. (1)

Recognition of the potential for error caused by similar drug name pairs has prompted regulatory authorities, patient safety organisations, the pharmaceutical industry and health professionals to develop strategies that seek to lower the risk of error while acknowledging challenges in the provision of health care. Health Canada recently revised its Guidance Document on the Review of Drug Brand Names (2) to provide greater direction to the pharmaceutical industry on the processes to follow when determining the potential for proposed names to be confused with those of other products on the Canadian market. Similarly, the FDA’s process for name review was developed from initiatives that aim to minimize the potential for medication errors. (3) These documents and processes address drug brand names under the authority of the regulator in granting approval for the marketing of health products.

International Nonproprietary Names (INN) may also be subject to look-alike sound-alike confusion. Unlike brand names, these names are selected by the WHO’s INN Programme. Many of the drug name pairs on ISMP’s list of confusable names are INNs. (4) In addition, the complexity of biological products and the application of technologies such as nanotechnology and pegylation has led to the use of drug names that pose challenges for error-free communication across all stages of the medication use process.
Trastuzumab and trastuzumab emtansine

In 2013 regulators including Medsafe, the FDA, and Health Canada issued safety communications (5, 6, 7) alerting health professionals to the potential for medication errors based on look-alike sound-alike confusion between two nonproprietary names1, trastuzumab (78) (40) and trastuzumab emtansine (103) (65). The communications directed health professionals to use the respective brand names of Herceptin® and Kadcyla® throughout the medication use process in order to reduce the risk of name confusion.

Trastuzumab emtansine (103)(65) represents the first example of an antibody-active drug conjugate for which the monoclonal antibody portion – trastuzumab – was previously marketed as a separate compound. The two INNs are both in use concurrently within health facilities. Differences in dose and treatment schedule (conjugate used at ±50 % of the antibody dose) make the correct use of these products critical. The Lists of Recommended and Proposed International Nonproprietary Names published by the INN Programme indicate that there are other monoclonal antibodies which may be available in the future both with and without conjugates, such as indusatumab (112)(74) / indusatumab vedotin (112)(74) and vorsetuzumab (107) (69) / vorsetuzumab mafodotin (107)(69). Antibody-drug conjugates have also been developed in which the same antibody is conjugated with different cytotoxic agents (e.g. cantuzumab mertansine (105)(65) and cantuzumab raviotansine (105)(66)). The number of look-alike and sound-alike INNs for monoclonal antibodies will naturally increase, with a corresponding greater risk of name confusion.

The examples in Table 1 illustrate that confusion between the antibody and the antibody-drug conjugate as well as between antibody-drug conjugates with

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Table 1. Sample list of antibody-active drug conjugates

<table>
<thead>
<tr>
<th>INNs</th>
<th>Active moieties*</th>
</tr>
</thead>
<tbody>
<tr>
<td>trastuzumab emtansine (103)(65)</td>
<td>Emtansine</td>
</tr>
<tr>
<td>vorsetuzumab mafodotin (107)(69)</td>
<td>Mafodotin</td>
</tr>
<tr>
<td>denintuzumab mafodotin (111)(73)</td>
<td></td>
</tr>
<tr>
<td>lorvotuzumab mertansine (103)(65)</td>
<td>Mertansine</td>
</tr>
<tr>
<td>cantuzumab mertansine (105)(65)</td>
<td></td>
</tr>
<tr>
<td>cantuzumab raviotansine (105)(66)</td>
<td>Raviotansine</td>
</tr>
<tr>
<td>indatuximab raviotansine (105)(67)</td>
<td></td>
</tr>
<tr>
<td>anetumab raviotansine (109)(71)</td>
<td></td>
</tr>
<tr>
<td>coltuximab raviotansine (109)(71)</td>
<td></td>
</tr>
<tr>
<td>brentuximab vedotin (103)(65)</td>
<td>Vedotin</td>
</tr>
<tr>
<td>enfotumab vedotin (109)(71)</td>
<td></td>
</tr>
<tr>
<td>polatuzumab vedotin (110)(71)</td>
<td></td>
</tr>
<tr>
<td>pinatuzumab vedotin (108)(70)</td>
<td></td>
</tr>
<tr>
<td>lifastuzumab vedotin (110)(72)</td>
<td></td>
</tr>
</tbody>
</table>

* See reference (8)

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either the same antibody or the same drug/toxin is possible. Errors relating to antibody-drug conjugates (cantuzumab mertansine (105)(65) vs cantuzumab ravidansine (105)(66)) could theoretically be even more dangerous than confusion between the antibody and the antibody-drug conjugate where toxicity or adverse effects are mainly related to the incorrect dose or lack of effect.

Antibody-active drug conjugates are named in accordance with the naming policy of the INN Programme in which a separate, second word identifies the conjugate. (9) Changing the order of the words so that the conjugate appears first would not mitigate the risk of name confusion as some drugs/toxins are conjugated to more than one antibody. In the case of trastuzumab emtansine (103) (65), regulators and healthcare providers have proposed strategies to address the possibility of confusion. These include the addition of a prefix (ado-trastuzumab emtansine) as well as specific prescribing, dispensing, labelling, systems and storage requirements.

FDA experience – does the addition of a prefix prevent errors?
During clinical trials prior to market authorization in the United States, four patients inadvertently received trastuzumab emtansine at 6 mg/kg instead of trastuzumab. It was reported that all four patients developed Grade 2 thrombocytopenia and increased liver transaminases. In one case a Holter monitoring 18 days after the error showed asymptomatic ventricular extrasystoles. The following day, the patient died. The cardiologist did not believe that the extrasystoles contributed to death. No autopsy was performed. (10)

As a result of these medication errors, the FDA took the step of modifying the approved nonproprietary name of the conjugated compound to ado-trastuzumab emtansine. The effectiveness of the addition of the prefix in preventing name confusion errors is difficult to determine at this date. Reports published shortly after the approval indicated that there were inconsistencies in the terminology used in U.S. drug information references as well as in health information systems, with some publications displaying the prefix ‘ado’ and others omitting it. It was postulated that health professionals may have encountered difficulties in accessing key information or placing orders for the drug. (11) Unilateral use of this strategy may also make cross-referencing of data or information retrieval by other regulatory authorities or organizations difficult. For example, some Canadian databases such as those used by poison control centres may rely on content from U.S.-based sources, and delays in retrieving information may occur if users do not enter the ‘ado’ prefix as part of their search criteria. The continued use of the ‘ado’ prefix may pose a challenge in light of the possibility of new conjugates as well as new monoclonal antibodies.

Roche/Genentech Global Safety Database
At the request of the INN Programme, Roche/Genentech performed a search of their Global Safety Database for post-market reports of medication errors between the two substances. The search looked for reports of (ado)-trastuzumab emtansine entered in the database until 21 February 2015 under the MedDRA High Level Group Term (HLGT) “Medication Error”. Although there was a lack of detail in the data provided, three
cases reported in the U.S. are suggestive of product confusion. A mix-up between trastuzumab and ado-trastuzumab emtansine cannot be excluded.

**EMA data**

According to the assessment report for marketing authorization from the EMA, "six cases of medication error occurred in the clinical trials. Of these 4 were due to a confusion between trastuzumab emtansine and trastuzumab. The medication error occurred with a product labeled for clinical trials, which had no tradename or specific distinguishing features to differentiate the two products."

Clinical consequences from these errors are not provided in the report. (12)

The post-market data from Roche/Genentech indicates that a total of 12 medication errors involving trastuzumab emtansine were reported until 21 February 2015 in the following countries of the European Union: Germany (7), Greece (2), United Kingdom (2) and Denmark (1). No further details regarding the role of name confusion were provided.

**Health Canada data**

As regards Canadian data, three cases were reported to Health Canada until March 31, 2015. The first report was received as a communication prior to the market authorization in Canada of trastuzumab emtansine under the brand name Kadcyla® in October 2013. The communication identifies the potential for selection errors during ordering, computer order entry, compounding and programming IV pumps.

The second report received describes a near-miss incident in which trastuzumab emtansine (Kadcyla®) was selected at order entry in the pharmacy software instead of trastuzumab (Herceptin®). The error was caught when the label generated by the computer was being checked for accuracy. The reporter indicated that limitations in systems had prevented the consistent use of the brand name as per the Health Canada safety communication.

The third report outlines a sequence of events that led to a patient receiving trastuzumab instead of trastuzumab emtansine. The prescription for trastuzumab emtansine was correctly entered into the pharmacy software and verified by the pharmacist. During compounding the technician inadvertently mixed the order using vials of trastuzumab and then labelled the product as trastuzumab emtansine. At the time of the incident, labels generated by the computer used only the nonproprietary name and did not include the brand name. The pharmacist did not catch the error and the drug was then given to the patient labelled as trastuzumab emtansine although it contained trastuzumab.

Later a technician observed extra stock of trastuzumab emtansine in the fridge, and the error was detected. The reporter stated that the same situation had occurred a week or so prior, but had been intercepted by the pharmacist before the patient received the drug.

The patient did not suffer any adverse effects from the error and was rescheduled to receive trastuzumab emtansine the following week, eventually resuming the originally planned schedule of administration on a three-week cycle.

The report revealed that the following changes were implemented as a result of the error and the near-miss:

- The order of the name in the pharmacy software was switched so that the brand name appears first (e.g. Kadcyla® – trastuzumab emtansine)
Labels affixed to the IV bags now include the brand name in addition to the INN.

The two medications are now stored separately.

A high-alert² colour-coded label has been added.

Additional risk mitigation strategies have been proposed to support the safe use of trastuzumab and trastuzumab emtansine including the following: (13)

- Recommended dosing and dose limits should be programmed into software at the point of order entry.
- Automated alerts and warning labels should remind practitioners that the medications are not interchangeable.
- Use of the brand names in addition to nonproprietary names should occur at each stage of the medication use process.

The market authorization holder has also provided training materials and other resources to health facilities to help minimize the risk for name confusion.

Conclusion

The influence of under-reporting on the voluntary reporting of medication errors and adverse effects is such that the rate of occurrence of these events cannot be effectively determined. The true incidence of errors between trastuzumab and trastuzumab emtansine is therefore not known, although the reported cases highlight the potential for serious harm from medication errors resulting from name confusion.

For the future, healthcare providers should continue implementation of a system-wide set of standard risk mitigation strategies that acknowledge risks at each stage of the medication use process. Challenges such as software limitations and diversity of processes will need to be addressed in recognition of the continued development of antibody-drug conjugates and the increased complexity of look-alike sound-alike name candidates. The use of brand names in addition to nonproprietary names for these antibody-drug conjugates during prescribing and dispensing as well as clearly distinguishable packaging and labelling would be key to preventing medication errors. Promotion of the INN as a standard for drug nomenclature is also important to ensure that health professionals understand its role and application. Other strategies such as the addition of a prefix or a suffix (e.g. a 4-letter biological qualifier) require further evidence of their effectiveness as patient safety measures.

References


² High-alert medications are drugs that bear a heightened risk of causing significant patient harm when they are used in error.


Quality of medicines

Quality of misoprostol products

This article presents findings from testing of misoprostol samples, specifically with regard to the percentage of labelled content of active ingredient over time in products packed in different types of blister packs, and makes recommendations for national regulatory authorities and for procurement organizations.

Background

Misoprostol was registered by GD Searle and Co (now part of Pfizer) under the brand name of Cytotec® for the prevention of gastric ulcers associated with non-steroidal anti-inflammatory drugs. There are now many generic misoprostol products available cheaply in low- and middle-income countries, and many (but not Cytotec®) are registered for obstetric indications. Misoprostol is on WHO’s Model List of Essential Medicines for use in the induction of labour, incomplete abortion, early abortion (with mifepristone), and for the prevention and treatment of post-partum haemorrhage (PPH) (1).

Misoprostol is a viscous oil, extremely susceptible to degradation. This is ameliorated by using a 1% dispersion of misoprostol in hydroxypropyl methyl cellulose (HPMC), which is considerably more stable and allows the manufacture of tablets with a shelf life of several years at room temperature (2). Nevertheless, exposure to water has been shown to be the principal driver in the degradation of misoprostol in tablets (3), and can occur during manufacture through the use of inappropriate excipients or inadequately controlled environmental conditions. Tablets can also be exposed to moisture depending on their packaging. Polyvinyl chloride (PVC) or polyvinylidene chloride (PVDC)/aluminium blister packs do not provide adequate protection against penetration by moisture, a double aluminium blister pack is therefore recommended (4).

In the past decade there has been a dramatic increase in availability and use of generic misoprostol products worldwide. In addition to its use in early abortion, the international community has been promoting its use in PPH. Unfortunately, this increased availability has not been accompanied by adequate control of the quality of generic products. This was first investigated in 2011 by Concept Foundation, Bangkok, Thailand, and its laboratory subsidiary, Health Concepts International (HCI), with the support of

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Gynuity Health Projects. More recently, studies have been conducted in Nepal and Nigeria and analyses have been performed for several international procurement agencies. This briefing note summarizes the results of both the early study and subsequent analyses undertaken by HCI.

Study design and methodology
In 2011, HCI analyzed 74 samples of misoprostol finished pharmaceutical products collected by Concept Foundation in Bangladesh, Egypt, Cambodia, Kenya, India, Mexico, Nigeria, Pakistan, Peru and Viet Nam. These samples were collected by random sampling from hospital clinics, pharmacies and drug sellers. In 2014-2015, an additional 141 samples collected in Nigeria, Nepal, Pakistan, Bangladesh, Argentina, Indonesia, Peru, the Philippines and Kazakhstan were analyzed. The 121 samples from Nepal and Nigeria were collected by convenience sampling under protocols following WHO guidelines (4) from public, social marketing and private sector service outlets, including warehouses, pharmacies, drug sellers, and hospital or clinic dispensaries. The remaining 20 samples were analyzed for the International Planned Parenthood Federation and Marie Stopes International and had been collected by random sampling from clinics or directly from manufacturers.

The tablets were stored below 30°C until analyzed, at which time the appearance of tablets and their packaging and manufacture dates were documented for all samples, their identity determined, and misoprostol assayed to assess percent of labelled content (LC).

In the absence of a pharmacopoeial method¹, Health Concepts International has developed an analytical method for misoprostol and its principal degradation product, A-type misoprostol, in line with its scope of work accredited under ISO/IEC 17025. The high performance liquid chromatography (HPLC) method was validated and shown to be in conformity with the standard operating procedures instituted under ISO17025:2005 (6). An Agilent HPLC system equipped with a multi-wavelength UV detector was used at a wavelength of 200 nm, with a Poroshell 120 EC-C8 column (4.6 x 75 mm, 2.7µm) and a mobile phase of methanol, water and acetonitrile ratio 40:35:25 v/v/v.

Findings
Of 215 samples analyzed, 119 (55%) were within specifications, containing 90-110% of the labelled content (LC) of 200µg misoprostol, 85 (40%) were below 90% of LC of which 14 contained no misoprostol at all, and 11 (5%) were between 110 and 121% of LC (due to manufacturers’ concern of degradation over time). The results are shown in Figure 1.

There were 14 samples of product which contained no misoprostol or any of its principal degradation products. Ten samples from one generic company contained no misoprostol and it is not known whether this was a falsified product or whether the issue was due to a quality assurance problem. One sample was from an unidentified manufacturer, and three samples were labelled as the innovator product, Cytotec® (collected in Cambodia, ¹ Note: A draft monograph on misoprostol tablets for inclusion in The International Pharmacopoeia has been posted for public comment (Working document QAS/15.643) and is included in the Consultation documents section of this issue of WHO Drug Information.
Nigeria and the Philippines); the latter were determined to be falsified products.

**Packaging**

Fifty samples were packaged in plastic/aluminium (plastic/alu) blister packs, one in a plastic bottle and 164 in aluminium/aluminium (alu/alu) blister packs.

Among the 50 samples packaged in plastic/alu 39 (78%) were out-of-specifications, including 38 samples below 90% LC, 27 below 60% LC and 18 below 30% LC.

Among the 164 samples packaged in alu/alu 58 (35%) were out-of-specifications, of these 47 were below 90% LC, 27 were below 60% LC and 14 were below 30% LC.

Interestingly, the sample packed in a plastic bottle was within specifications.

**Degradation over time**

After one year none of the 30 samples packaged in plastic/alu were within specifications, while degradation had occurred in 32 (28%) of 116 samples packaged in alu/alu; the other 84 (72%) were still above 90% LC.

**Discussion**

The results demonstrate the necessity of packaging in alu/alu blister packs. Nevertheless, packaging in alu/alu in itself is not a guarantee of lack of degradation – 28% of the alu/alu samples showed degradation. Work undertaken by Concept Foundation with manufacturers has shown that if the manufacturing process is not undertaken appropriately and the environment adequately controlled,
humidity may enter the alu/alu blister, causing degradation to occur.

The results did confirm that quality-assured misoprostol products can be manufactured. A total of 51 samples were labelled as products that had passed a stringent assessment, including 41 misoprostol samples manufactured by the innovator and approved by an SRA (three of these samples were determined to represent falsified products), five samples of an SRA-approved mifepristone & misoprostol combination pack, three samples of WHO-prequalified misoprostol and two samples of misoprostol with an Expert Review Panel rating allowing time-limited purchase. Excluding the three samples of falsified product labelled as the innovator product, a total of 48 samples represented stringently assessed products. Of these, one was below 90% LC and two were slightly above 110% LC.

**In summary:**

► Four out of every ten samples contained less than 90% of the labelled content of misoprostol.
► None of the 50 samples packed in a plastic/alu blister was within specifications after one year.
► Misoprostol packaged in an alu/alu blister pack is not a guarantee of a stable product – 28% of the alu/alu samples showed degradation.
► There was no evidence that 14 samples had ever contained misoprostol, three of these were falsified products labelled as Cytotec®.
► Only one of 48 samples of products that had passed a stringent assessment had a labelled content of misoprostol below specifications.

**Recommendations**

**For national authorities**

It is essential that a survey of products available in the country is undertaken and sub-standard products removed from the market.

**For procurers**

Product in PVC or PVDC/aluminium blister packs should never be purchased. It has been documented that they allow moisture to enter the blister pack, and no product analyzed met specifications after one year.

It is essential to obtain evidence of the quality, and in particular, the stability of product from the manufacturer before ordering. Preshipment testing is pointless for inappropriately manufactured and packaged product – the product may comply with specifications shortly after manufacturing but may only have 50% of labelled content within six months.

As quality-assured products (prequalified by WHO or approved by an SRA) become available, national and international procurers should ensure that they purchase these products.

**References**


5 WHO. Guidelines on the Conduct of Surveys of the Quality of Medicines. Working document No. QAS/15.630. Adopted by the Expert Committee on Specifications for Pharmaceutical Preparations at its 50th Meeting with amendments as agreed during the meeting.

Prequalification

WHO rotational fellowships: an update

WHO prequalification has a significant impact on regulatory capacity in Member States. Much of the capacity-building effect has been achieved through the rotational positions offered by the WHO Prequalification Team (PQT), featured in an earlier issue of this journal. This article provides an update on the rotational fellowships programme.

Background
Access to medical products of assured quality, safety and efficacy is one of the cornerstones of health care. The essential role of WHO prequalification in facilitating procurement of products of assured quality, safety and efficacy has been recognized (1). What is less well known is the significant capacity-building effect that prequalification has in WHO Member States.

Much of PQT’s capacity-building effect is due to the inclusive character of its work. Since its inception in 2001, the medicines prequalification programme has carried out its evaluations together with experts from around the world, bringing in the perspectives from both mature regulatory authorities and developing countries. In addition, PQT develops training programmes, conducts regulatory trainings in countries and in Copenhagen, supports regulatory collaborations, facilitates regulatory approvals, organizes consultations and provides technical advice.

An important part of this capacity-building framework are the rotational positions at PQT, a unique arrangement within WHO. These positions are offered to regulators who have had some initial exposure to PQT’s work. For medicines assessors, the bi-monthly assessment sessions in Copenhagen – where prequalification dossiers for pharmaceutical product are evaluated by regulatory experts from around the world – are the training ground from which rotational assessors are recruited after 1-2 years of participation.

Feedback obtained in 2012 indicated that the rotational fellowships enabled the regulators to become familiar with international standards and procedures and to build professional networks. After their return they implemented guidelines and procedures in line with WHO standards in their countries, with a positive

We thank the following regulators for their feedback: Anita Bitegeko, Felix Chizu, Donatien Kabamb Kabey, Hilton Katz, Chinyere Ilonze, Kate Kikule, Sunday Kisoma, Nkaelang Modutlwa, Tinashë Muvinimi, Andrew Okello Okonye, Makomani Siyanga, Uchenna Sonny-Afoekelu and Zhang Hua.

We gratefully acknowledge the financial contributions from UNITAID; U.S. FDA; Gavi, the Vaccine Alliance and WHO’s Pandemic influenza preparedness (PIP) programme, that helped to make the rotational fellowship programme a success. We also thank the Bill & Melinda Gates Foundation; the Global Fund to Fight AIDS, Tuberculosis and Malaria; the World Bank; the United Nations Population Fund (UNFPA) and others for their contributions to capacity-building activities offered by PQT.
impact on client satisfaction, regulatory control and work-sharing initiatives (2).

Another round of feedback was sought from regulators who have held a rotational position at any time since 2014 as a basis for the update presented here.

**An expanding network**

Since 2006, a total of 37 rotations have taken place. Starting with medicines assessors, the programme was opened up to inspectors in 2014 and to vaccines assessors in 2015 (Table 1). The first pharmacovigilance rotation is expected to start in June 2016, and rotations for regulatory systems strengthening are also intended to be introduced.

At the time of writing 36 of the 37 regulators that have held a rotational post were still in professional contact with PQT; 28 were working at national medicines regulatory authorities (NMRAs) and eight at international organizations (Figure 1).

Given that English is the working language at WHO there has been a predominance of fellows from anglophone countries. However, participation from non-English-speaking countries has increased in recent years, with a total of five inspectors from China and Brazil and two assessors from the Democratic Republic of Congo (DRC) completing a rotation. This has helped to expand the PQT network. DRC became the second of six French-speaking countries to

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**Table 1. Rotational fellowships at WHO-PQT**

<table>
<thead>
<tr>
<th>Type of rotation</th>
<th>Duration</th>
<th>First rotation started</th>
<th>Total rotations to date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessors (medicines)</td>
<td>3 months</td>
<td>November 2006</td>
<td>28</td>
</tr>
<tr>
<td>Inspectors</td>
<td>4 months</td>
<td>March 2014</td>
<td>7</td>
</tr>
<tr>
<td>Assessors (vaccines)</td>
<td>3 months</td>
<td>July 2015</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>37</strong></td>
</tr>
</tbody>
</table>

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**Figure 1. Current places of work of former rotational fellows**

As at February 2016 (in brackets: number of regulators)

- UNFPA (1)
- WHO-PQT (5)
- NMRAs of: Ethiopia (1), Tanzania (5), Uganda (4), Zimbabwe (3), Zambia (2), Botswana (1), South Africa (1), USP (2), ANVISA Brazil (1), Center for Food and Drug Inspection (CDFI)/CFDA China (4)

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**Figure 1**

[Map showing current places of work of former rotational fellows]

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**NMRA** National medicines regulatory authority

**USP** United States Pharmacopeia

**UNFPA** United Nations Population Fund
participate in the collaborative registration procedure for WHO-prequalified products (3) and the regulatory authority of the DRC hosted the 2015 annual meeting of focal points, which was combined with a PQT regulatory training attended by assessors from nine francophone African countries.

**Benefits**

PQT is benefiting from its growing network of experts as it is increasingly able to draw on the expertise of assessors and inspectors throughout the countries where WHO-prequalified medicines are used. After their rotations, the assessors continued to contribute to the assessment sessions held in Copenhagen and regional capacity-building events. The inspectors participated in PQT inspections and conducted supportive activities in their countries such as verification of corrective and preventive action (CAPA), investigation of complaints and monitoring of progress of local manufacturers after provision of PQT technical assistance.

The benefits for individual regulators and their organizations, as mentioned in the feedback received from the rotational fellows, are outlined below.

**Convergence of standards**

During their rotation, the regulators participated in a wide range of prequalification activities and were provided with a complete set of the WHO norms and standards that underpin prequalification. This enabled them to reconsider regulatory practices in their countries. A rotational inspector said:

“I learned WHO GMP guidelines systematically. It could help me realize the gaps between WHO and China GMP guidelines. Hence, as I will be involved in the revision of China GMP for CFDA in the near future, I will know how to achieve the harmonization of these guidelines.”

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**Box 1: ‘Critical mass’ for change**

Capacity-building is a gradual process, as illustrated by these two examples of comments by rotational assessors about challenges experienced after their return.

The first rotational fellow from Zambia worked at WHO in 2010. As a result of his authority’s participation in WHO prequalification, including his rotational fellowship, the Medicines Committee of the Board directed the regulatory authority to urgently start applying unified standards. In his 2012 feedback he said:

“The difficult part during my subsequent work has been to achieve a complete overhaul of the registration system to bring it in line with international best practices. (…) This involves availability of resources and skilled staff, requiring a sound financial base.”

The first rotational fellow from Tanzania completed his rotation in 2007. In 2011 he became Director General of the regulatory authority, and two assessors who had completed rotational fellowships at PQT in 2008 and 2010 moved to senior management posts. A fourth assessor completed a rotation in 2015. He said:

“Coming back home from the fellowship was a smooth transition since the minimum framework for regulation of medicines was already in place, hence I did not experience much difficulty in implementation of best practices.”
**Links with WHO**

The rotational fellows attended the WHO induction course, visited all units within the Essential Medicines and Health Products Department and collaborated with other departments as needed. For example the rotational inspector from Brazil provided input on the Zika virus disease emergency. The regulators appreciated the opportunity to get to know the work of WHO, be exposed to a different job environment and make contacts for future professional networking and information-sharing.

**Sustained impact over time**

The two rounds of feedback received from former rotational fellows suggest that implementation of WHO standards in countries has been progressing over time (see also examples in *Box 1*). In countries with less mature regulatory systems a framework was put into place covering the main functions. Thus in DRC ministerial decrees on registration, sales and outlets of medicines were signed, guidelines on good manufacturing practice and marketing authorization applications were adopted, and a national medicines registration committee was formed. Consequently, most of the assessment procedures changed.

At authorities where a basic framework was already in place more advanced elements were added. In Botswana a guideline on Common Technical Document (CTD) format drafted by a returning rotational fellow was piloted and adopted within less than a year of his return. In Uganda submission of dossiers on active pharmaceutical ingredients (APIs) became a requirement for marketing authorization of medicines, with a former rotational assessor being appointed as the focal point for API evaluation. In Tanzania a rotational assessor introduced a shared repository of API assessment reports, saving evaluation time for relevant applications and allowing the evaluators to focus on issues related to the finished pharmaceutical products.

**Building regulatory capacity in countries**

All the respondents reported having shared their experience with other regulators, applicants and professional organizations during trainings, workshops and seminars. Review and discussion of particular applications were also an effective way to improve the review process, as suggested in this statement: “Assessors in my agency have learnt a lot from my experience gained during the rotation at WHO, so this has translated into quicker decision-making in terms of the right questions to ask applicants, and also in terms of registration of products.”

In the two rounds of feedback assessors from six countries said that they shared their knowledge and experience through peer review of assessment reports – an approach recommended in recent international guidance (4).

**Reliance and work-sharing**

Having worked with regulatory experts from all over the world, the regulators became more inclined to rely on other regulatory authorities’ decisions. Expedited review procedures for stringently assessed products were introduced in a number of countries. In terms of inspections, a rotational fellow stated:

“Exposure to the WHO and its collaborating partners (...) will also aid further collaboration (...). For instance, having joint inspections for common products and sites at national and
regional level and sharing information (...) will save resources in terms of finances, technical staff and time.” Work at WHO furthermore provided opportunities for involvement in advocacy at the international level to promote convergence, reliance and regional networks:

“I participated in the 17th ICDRA1 planning meeting (...). This is the first time ICDRA will be held in Africa. NAFDAC and other drug regulatory authorities in the region are expected to leverage this opportunity (...) by strengthening their medicines regulatory harmonization which was launched recently in Ghana.”

Progress in collaborative initiatives
Contributions to collaborative initiatives were mentioned more frequently in this round of feedback than in 2012, as for example in this statement:

“I wrote a proposal for strengthening joint GMP inspections within the EAC region with support from international agencies and experts, which was approved by the EAC and is currently under implementation.”

Former rotational fellows have been driving forces in collaborative projects. The three initiatives mentioned in their feedback have all progressed well in recent years:

• The East African Community (EAC) harmonization project has resulted in introduction of harmonized guidelines and requirements in EAC countries (5). Joint inspections are conducted, and the regulatory authorities have embarked on joint assessments of product dossiers.

• The Zazibona collaborative pathway for registration of essential medicines in Zambia, Zimbabwe, Botswana and Namibia (6) has enabled significant work-sharing. A former rotational fellow now working at PQT facilitates the information-sharing process. Since 2013 over a hundred submissions have been assessed, leading to 69 registrations in participating countries (7).

• The WHO collaborative registration procedure for WHO-prequalified products aims to shorten registration timelines through sharing of PQT assessment and inspection reports. A total of 110 marketing authorizations have been granted through this procedure since 2013 (3), the median time to registration was 78 days. Ten former rotational fellows have been serving as collaborative registration focal points at NMRAs.

Challenges
All the regulators felt that the rotations were too short to cover the full range of WHO activities on medicines regulation. They wished to continue being involved in prequalification activities, for example in evaluating applications for snake venoms, which are newly eligible for prequalification. Several suggested that a continuous development programme should be introduced. Considering the growing number of applications for biosimilars and vaccines, the wish was expressed that WHO should provide more support to NMRAs in these areas as well.

The regulators’ comments about challenges on their return were mainly related to the resource constraints that continue to affect many regulatory authorities in WHO Member States. One respondent mentioned the heavy work load, leaving little time to implement

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1 International Conference of Drug Regulatory Authorities, see www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra/en/
change. Two noted the need to advocate for more staff and adequate salaries, and one mentioned the lack of a qualified laboratory and the difficulty of transforming the NMRA’s business model for more managerial and financial autonomy.

Applicant-related challenges were mentioned by one respondent, who said that numerous applications were still being submitted that were not in the CTD format, causing delays in registration.

Conclusion
The rotational fellowship programme at WHO-PQT continues to have a positive impact at regulatory authorities. It has strengthened the network of people who work together to improve medicines regulation from a public health perspective.

Given the increasing complexities of medicines regulation the World Health Assembly has urged WHO Member States to engage in networks, pool regulatory capacities and promote collaboration and information-sharing across countries (1). The PQT rotational fellowship programme provides a platform for learning and sharing of experience, bringing regulators together to deal with some of the challenges that medicines regulation will continue to pose globally and in each of their countries.

References
3 WHO Prequalification Programme [web site]. Collaborative registration.
7 Collaboration in registrations: WHO Prequalification Team. Presentation made during the Joint WHO-UNICEF-UNFPA Meeting with pharmaceuticals and diagnostics manufacturers and suppliers, 23-26 November 2015, Copenhagen, Denmark.
Safety news

Restrictions

Nicorandil: Use only as second-line angina treatment
United Kingdom – The MHRA has advised health professionals that nicorandil should only be used as second-line treatment for stable angina when patients do not sufficiently respond to, do not tolerate or should not take medicines such as beta-blockers and/or calcium antagonists. Nicorandil can cause serious skin, mucosal, and eye ulceration, including gastrointestinal ulcers which may progress to perforation, haemorrhage, fistula, or abscess. Treatment with nicorandil should be stopped if ulceration occurs, and alternative treatment or specialist advice considered if angina symptoms worsen. (1)

This advice reflects harmonized product information, labelling and package leaflets for nicorandil (Ikorel®, Dancor® and associated names) across the European Union as recommended by EMA in March 2015. The harmonized product information also includes updated advice on the medicine’s posology, contraindications and precautions for use. (2)

(2) EMA. Questions and answers on Ikorel, Dancor and associated names (nicorandil, 10 and 20 mg tablets). 5 June 2015.

Fosamprenavir: contraindicated with paritaprevir
European Union – A new contraindication has been added to the approved product information of the antiretroviral medicine fosamprenavir (Telzir®). The medicine should not be co-administered with paritaprevir due to the expected increase of paritaprevir exposure and the lack of clinical data assessing the magnitude of this increase.


Ombitasvir / paritaprevir / ritonavir: extended contraindication
Japan – The PMDA has extended the contraindication for the antiviral combination ombitasvir hydrate/paritaprevir hydrate/ritonavir (Viekierax®) to include patients with moderate liver impairment (patients Child-Pugh Class B) in addition to those with severe liver impairment (Child-Pugh Class C). A warning has been added to the product information that blood bilirubin level may significantly increase, and hepatic failure may be observed along with ascites, hepatic encephalopathy and other effects. Patients should be carefully monitored. If any signs of liver failure are observed the drug should be discontinued and appropriate measures adopted.


Erlotinib: only for certain types of non-small cell lung cancer
European Union, New Zealand – Results of a recent study have indicated that erlotinib (Tarceva®) is only of benefit
in the first line maintenance treatment of non-small cell lung cancer in patients whose tumours harbour an EGFR-activating mutation. Product information updates have been recommended accordingly by a number of regulatory authorities (1, 2, 3).

(2) EMA Summary of opinion (post authorization), 17 December 2015.

Safety warnings

Thalidomide: reduced starting dose in patients over 75 years
United Kingdom – In line with EMA recommendations, the MHRA and the marketing authorization holder have informed health professionals that the starting dose of thalidomide has been reduced to 100 mg/day in patients over 75 years, to minimize the risk of adverse drug reactions.

Thalidomide combined with melphalan and prednisone is indicated as first-line treatment of certain patients with untreated multiple myeloma. The starting dose of melphalan in patients over 75 years of age should be 0.1–0.2 mg/kg daily, according to baseline bone-marrow reserve and renal function. Prescribers should be aware that even with a reduced starting dose of thalidomide, this age group may be at higher risk of serious adverse reactions than younger patients.

► Drug Safety Update volume 9 issue 5, December 2015: 1.

Nintedanib: avoid in hepatic function disorder
Japan – The PMDA has recommended that the use of nintedanib (Ofev®) should be avoided in patients with moderate to severe hepatic function disorder (Child-Pugh B and C) unless treatment with this drug is deemed necessary. The results from the clinical pharmacokinetic study, which was ongoing at the time of approval, showed that blood concentration of nintedanib ethanesulphonate increased in patients with hepatic function disorder.

Nintedanib is used to treat idiopathic pulmonary fibrosis. Approved product information in the United States and the EU states that the medicine is not recommended for use in patients with moderate to severe liver problems as it has not been studied in these patients.


Lenvatinib: tumour haemorrhage
Japan – The PMDA has warned that lenvatinib (Lenvima®), approved for the treatment of unresectable thyroid cancer, may cause carotid arteries haemorrhage or tumour haemorrhage associated with tumour shrinkage or necrosis. Furthermore, there have been case reports of development of massive bleeding from exposed carotid artery sites or fistula formulation sites. There is a risk of haemoptysis or haematemesis in patients with a tracheal fistula or oesophageal fistula.

The medicine should be used with caution in patients with tumour invasion in the carotid arteries, veins or other sites; this is seen in many patients with anaplastic thyroid cancer. Patients should be carefully monitored during
administration of the drug, and the presence or absence of fistula formation should be confirmed. In case of haemorrhages, administration of lenvatinib should be discontinued as necessary and appropriate measures taken.


Biphosphonates: very rare osteonecrosis of external ear canal

United Kingdom – The MHRA has advised health professionals to consider the possibility of osteonecrosis of the external auditory canal in patients receiving bisphosphonates who present with ear symptoms, including chronic ear infections, and in patients with suspected cholesteatoma. Possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma. Patients should be advised to report any ear pain, discharge from the ear or an ear infection during bisphosphonate treatment.

Evidence from the clinical literature and from reported cases supports a causal association between bisphosphonates and osteonecrosis of the external auditory canal. Product information for bisphosphonates available in the United Kingdom (alendronic acid, ibandronic acid, pamidronate disodium, risedronate sodium, sodium clodronate and zoledronic acid) has been updated.


Atovaquone: agranulocytosis and leukopenia

Japan – Following 11 reported cases of agranulocytosis and leukopenia in patients treated with atovaquone, including two fatal cases and five others for which causality could not be ruled out, the PMDA has recommended that product information for atovaquone-containing products (Samitrel®, Malarone®) should be updated to include this risk. Patients should be carefully monitored. If any abnormalities are observed, atovaquone should be discontinued and appropriate measures adopted.


MHLW Revisions of precautions and PMDA Summary of investigation results. 12 January 2016.

SGLT-2 inhibitors: ketoacidosis and urinary tract infections

United States of America – Following its drug safety communication of 5 May 2015, the FDA has added warnings to the product information for the sodium-glucose cotransporter-2 (SGLT2) inhibitors canagliflozin, dapagliflozin, and empagliflozin. These antidiabetics can cause ketoacidosis and serious urinary tract infections. Ketoacidosis can occur even if the blood sugar level is not very high. If ketoacidosis is suspected, the SGLT2 inhibitor should be discontinued and treatment instituted promptly. (1)

European Union – The EMA has made recommendations to minimize the risk of diabetic ketoacidosis associated with SGLT2 inhibitors, including in atypical cases where blood sugar levels are not as high as expected.

Patients should be made aware of risk factors and symptoms of ketoacidosis and should be asked to contact their health
care professional if they have any of these symptoms. If diabetic ketoacidosis is suspected or confirmed, treatment should be stopped immediately and should only be re-started if another cause for the ketoacidosis is identified and resolved. Caution should be exercised in patients with risk factors for ketoacidosis, which include a low reserve of insulin-secreting cells, conditions that restrict food intake or can lead to severe dehydration, a sudden reduction in insulin or an increased requirement for insulin due to illness, surgery or alcohol abuse. In patients hospitalized for major surgery or serious illness SGLT2-inhibitor treatment should be stopped temporarily.

Health professionals have been reminded that these medicines are only authorized for treating type 2 diabetes, not type 1 diabetes.

► (1) FDA Drug Safety communication, 4 December 2015.
   (2) EMA Press release, 26 February 2016.
   See also: Medsafe Prescriber Update 36(4): 57-58, December 2015

Elvitegravir/cobicistat/emtricitabine/tenofovir: interactions with anticonvulsants
Japan – The PMDA has recommended that the antiviral combination elvitegravir/cobicistat/emtricitabine/tenofovir (Stribild®) should not be administered concomitantly with anticonvulsants such as carbamazepine, phenobarbital, phenytoin or fosphenytoin. Approved product information in the EU includes a contraindication in patients treated with these anticonvulsants.


Nivolumab: diabetes mellitus and ketoacidosis
Japan – The PMDA has recommended updates to the product information of cancer medicine nivolumab (Opdivo®) to warn about the risk of type 1 diabetes mellitus – including the fulminant type – and diabetic ketoacidosis. Patients should be monitored for symptoms such as thirst, nausea and vomiting or increase in blood glucose levels. If type 1 diabetes mellitus is suspected, nivolumab should be stopped and appropriate measures taken, such as administration of insulin.

Product information in the EU mentions diabetes mellitus and ketoacidosis as uncommon adverse effects.


Natalizumab: new measures to manage PML
European Union – The EMA has recommended new measures to minimize the risk of progressive multifocal leukoencephalopathy (PML) with the multiple sclerosis medicine natalizumab (Tysabri®). PML is a rare and very serious brain infection caused by John Cunningham (JC) virus.

Patients considered as being at high risk for PML are those who were treated with immunosuppressants before starting natalizumab and have antibodies against JC virus and have been on natalizumab for more than two years. For these patients more frequent MRI scans (e.g. every 3-6 months) should be considered to enable detection and early treatment of asymptomatic cases, thus limiting the degree of potential brain damage. In these patients, treatment with natalizumab...
should only be continued if benefits outweigh the risks.

In patients who have not been treated with immunosuppressants before starting natalizumab, the level of antibodies (index) relates to the level of risk for PML. The antibody test should be repeated every 6 months in patients who tested negative, as well as those with antibody index values of 0.9 or less once they have been on natalizumab for longer than two years. Patients with index values above 1.5 and on treatment for longer than two years are considered to be at higher risk for PML and should be managed as described above.

If PML is suspected at any time, treatment with natalizumab must be stopped until PML has been excluded. ► EMA Press release, 26 February 2016.

Fingolimod: new measures to minimize PML and BCC risks
European Union – The European Medicines Agency (EMA) has recommended new monitoring measures to minimize the risks of progressive multifocal leukoencephalopathy (PML) and basal cell carcinoma related to the immunosuppressive effect of the multiple sclerosis medicine fingolimod (Gilenya®).

PML has been reported in patients treated with fingolimod, including in some not previously treated with another immunosuppressive medicine. A baseline MRI scan should be available usually within three months of starting treatment. If PML is suspected, MRI should be performed immediately and fingolimod should be stopped until PML has been excluded. If an anti-JC virus antibody test is done, it should be considered that the presence of lymphopenia may possibly affect the outcome, and that JC virus infection may still occur after a negative test.

With regard to the risk of basal cell carcinoma, a medical evaluation of the skin is recommended before starting treatment with fingolimod, after at least one year and then at least yearly. Fingolimod must not be used in patients with basal cell carcinoma or any other type of cancer. Patients should be instructed to look for signs of basal cell carcinoma and seek medical advice if they occur. Patients should be referred to a dermatologist if they have lesions suggestive of BCC.

► (1) EMA Press release, 18 December 2015.

Methylphenidate: hepatic failure
Japan – Following reports of hepatic failure and hepatic function disorder in patients treated with methylphenidate tablets (Concerta®, Ritalin®) outside Japan, the PMDA has reviewed available data, and the Ministry of Health, Labour and Welfare (MHLW) has recommended revisions to the package insert.

Product information approved in the UK lists hepatic enzyme elevations as rare, and abnormal liver function including hepatic coma as very rare adverse effects.

► MHLW Revisions of precautions and PMDA Summary of investigation results, 16 February 2016.

Varenicline: psychiatric symptoms and potential alcohol interaction
Australia – The TGA has recommended updates to the product information for the smoking cessation medicine varenicline (Champix®) to strengthen the warnings about the risk of psychiatric symptoms which may include depression, anxiety, agitation, aggression, mood swings, self-harm, thoughts of self-harm, or seeing,
hearing or sensing things that are not there. Alcohol consumption may increase these risks. Patients experiencing such symptoms should stop taking varenicline and contact a health professional immediately. The TGA will continue to monitor the issue.

► TGA Safety advisory, 2 December 2015.

**Label changes**

**Posaconazole: dosing of oral formulations not interchangeable**

**United States of America** – The FDA has approved labelling changes to help prevent dosing errors when switching between the oral suspension and delayed release tablet formulations of the antifungal medicine posaconazole (Noxafil®). Wording has been added to indicate that these two formulations cannot be directly substituted for each other but require a change in dose.

Since November 2013, the FDA has received eleven reports of the wrong oral formulations being prescribed and/or dispensed to patients. One case resulted in death, another in hospitalization.


**Unchanged recommendations**

**Rivaroxaban: clinical trial conclusions maintained**

**European Union** – The European Medicines Agency (EMA) has concluded that the benefit-risk balance of rivaroxaban in patients with non-valvular atrial fibrillation remains unchanged, despite a defect with the international normalised ratio (INR) device used in the main clinical study supporting its use. The study compared rivaroxaban with warfarin. There were concerns that the defective INR device could have provided lower INR values in some patients in the warfarin group, potentially leading to dose increases and therefore a higher risk of bleeding. After further data analyses the EMA’s Committee for Medicinal Products for Human Use (CHMP) concluded that the defective device would have had only a marginal effect on the study results and the conclusions would not be affected. Data from other large studies confirmed the comparative safety of rivaroxaban and showed similar rates of bleeding in their warfarin groups.


FDA restrictions for rosiglitazone had been removed in 2013 since data did not demonstrate an increased risk of heart attack compared to metformin and sulfonylurea. The training requirements have been fulfilled, and no new pertinent safety information has been identified.

► FDA Drug safety communication, 16 December 2015.

**Rosiglitazone: Risk Evaluation and Mitigation Strategy eliminated**

**United States** – The FDA has eliminated the Risk Evaluation and Mitigation Strategy (REMS) requiring manufacturers to provide educational training about the cardiac risks of rosiglitazone-containing type 2 diabetes medicines (Avandia®, Avandamet®, Avandaryl®, and generics). Data from other large studies confirmed the comparative safety of rivaroxaban and showed similar rates of bleeding in their warfarin groups.

Pharmaceuticals from Tianjin City region: potential contamination

United States of America – The FDA has alerted drug compounders and manufacturers that drug shipments from Tianjin, China are at risk of chemical contamination as a result of two massive explosions at a chemical warehouse of Tianjin Dongjiang Port Ruihai International Logistics Co. in August 2015. More than 40 different types of chemicals were discovered at the blast site.

Increased FDA surveillance resulted in the detection of hydrogen cyanide contamination in two shipments of drugs from Tianjin Tianyao Pharmaceuticals Co. Ltd located approximately 30 kilometres from the explosion site. The shipments were stopped, and the FDA is working with the Chinese Food and Drug Administration (CFDA) on the issue. Hydrogen cyanide was not detected in two other drug shipments sent to the United States by the same company since the explosion.

The FDA has reminded pharmaceutical companies that it is their responsibility to know the source of the ingredients and finished products that they obtain, and to
take appropriate precautions to ensure their quality.
► CDER Alert, 22 December 2015.

Baclofen active pharmaceutical ingredient: potential contamination
United States of America – The FDA has warned that baclofen active pharmaceutical ingredient (API) from Taizhou Xinyou Pharmaceutical & Chemical Co. Ltd, China, may be at risk for contamination with particulates and should not be used to manufacture or compound sterile injectable drugs.

The FDA has informed compounders in the United States that injectable products compounded with the affected API could pose serious safety risks, especially when administered directly into the spinal column. They may also clog pumps used to administer the medication. There is a potential risk that the baclofen API may be contaminated by endotoxin or microorganisms. The FDA is continuing to investigate this incident. (1)

Australia – The TGA has determined that none of the products included on the Australian Register of Therapeutic Goods contain the baclofen API manufactured by Taizhou Xinyou Pharmaceutical & Chemical Co. Ltd. However, it has been used by some Australian compounders. The TGA has advised that this API should not be used to compound sterile injectable medicines. (2)

► (1) FDA Statement, 9 December 2015.
(2) TGA Medicines Safety Update Volume 7 Number 1, February 2016.

Notice of concern for Cadila Healthcare Ltd
Geneva – The WHO prequalification team has informed the public that issues considered of concern have been noted in a GMP inspection conducted on 26–30 October 2015 at Cadila Healthcare Limited, Ahmedabad, Gujarat, India as part of the WHO Prequalification Vaccine evaluation and monitoring process.

A Notice of Concern (NOC) was therefore issued to the company. The company immediately stopped production, initiated an internal investigation and initiated a voluntary recall of all the batches of its Lyssavac-N® anti-rabies vaccine manufactured after April 2015, from when investigation revealed the critical issue could have started. The company has also informed WHO that the suspended manufacturing activities for vaccines and biologicals at this site will only resume after acceptable corrective and preventative actions (CAPA) have been submitted, assessed and effectively implemented as confirmed through an onsite inspection.

The full notice of concern is available at www.who.int/entity/immunization_standards/vaccine_quality/NOC_CadilaFebruary2016.pdf?ua=1.
Falsified product alerts

It is necessary to ensure that all medical products are obtained from authentic and reliable sources. Their authenticity and origin should be carefully checked and verified with manufacturers before use. WHO requests increased vigilance for the supply chains of countries likely to be affected by the falsified products mentioned below.

Phenobarbitone

Falsified phenobarbitone tablets circulating in West Africa

This Medical Product Alert relates to the circulation of falsified versions of phenobarbitone (also known as phenobarbital) in West Africa. Phenobarbital is used as a treatment against epilepsy and is frequently dispensed free of charge in community-care health centres.

In December 2015, the Liberia Medicines and Health Products Regulatory Authority (LMHRA) notified WHO of two suspect products that supposedly contain tablets of 100 mg of phenobarbitone. These products were detected through a lack of efficacy (patients treated for epilepsy had an increased recurrence of seizures during the course of their treatment with these products).

- **Product Name:** Phenobarbitone
- **Batch Number:** 2081
- **Manufacturing Date:** 7-2012
- **Expiry Date:** 6-2016
- **Manufacturer:** Mejoc Pharm and Chemical

The manufacturer name only appears on one of the two types of containers shown in the photographs included in the WHO Medical product alert. The name and address of the manufacturer does not exist, and the labelling contains spelling errors. Investigation of the WHO SSFFC Medical Products database identified that a similar product was found in Guinea Bissau in 2013, with almost identical packaging and labelling and bearing the same batch number, a manufacturing date of 7-2010 and an expiry date of 6-2014. The packaging also contains spelling mistakes. A photograph is provided in the WHO medical product alert.

The product found in Guinea Bissau was tested by an independent laboratory, and analysis indicated that the product contained no active pharmaceutical ingredient. Authorities in Guinea Bissau had been notified. This product was also detected through a lack of efficacy (patients treated for epilepsy had an increased recurrence of seizures during the course of their treatment with these products).

►WHO. Medical Product Alert N° 1/2016, 5 February 2016 (includes photographs).

Yellow fever vaccines

Falsified AMARIL yellow fever vaccines circulating in South East Asia

This Medical Product Alert relates to the confirmed circulation of falsified versions of "AMARIL stabilised vaccine" in South East Asia.

This vaccine is used to immunise against yellow fever and is a WHO-prequalified product. Yellow fever vaccine is on the WHO list of Essential Medicines. On 9 February 2016, the Pasteur Institute in Dakar, Senegal, informed WHO that they had identified a falsified version of their “AMARIL stabilised vaccine” circulating in Bangladesh.
Genuine AMARIL vaccines and solvents are manufactured by the Pasteur Institute in Dakar, Senegal. The Pasteur Institute in Dakar has confirmed that there are a number of falsified elements on the packaging, including a falsified expiry date, as well as other inconsistencies that were identified through visual inspection of photographs of the falsified products as compared to the genuine products. Laboratory analysis is pending.

- **Product Name:** AMARIL stabilised yellow fever vaccine
- **Batch Number:** 2265
- **Expiry Date:** June 2017
- **Stated manufacturer:** Pasteur Institute in Dakar

No serious adverse reactions attributed to this falsified vaccine have been reported at this stage.

► WHO. Medical Product Alert N° 2/2016, 11 February 2016 (includes photographs).

### Hepatitis C medicines

**Falsified Hepatitis C medicines circulating in South East Asia**

This Medical Product Alert relates to the circulation of confirmed falsified versions of Sofosbuvir 400mg + Ledipasvir 90mg and Daclatasvir 60mg in South East Asia. Both products are used to treat Hepatitis C. Daclatasvir 30mg and the fixed dose combination of Sofosbuvir 400mg + Ledipasvir 90mg are on the WHO list of Essential Medicines.

In February 2016, WHO was informed by a local NGO working in Myanmar that they had identified falsified versions of the following two products:

- **Product Name:** LEDSO capsules DAKAVIR
- **Batch Number:** 0022 0322
- **Expiry Date:** 4/2017 4/2017
- **Date of manufacture:** 5/2015 5/2015

Both products claim to be manufactured by PHARCO Corporation, Alexandria, Egypt.

Laboratory analysis is pending so as to better assess the threat posed to public health. PHARCO Corporation has stated that:

- they do not manufacture the specific fixed dose combination of Sofosbuvir 400mg + Ledipasvir 90mg
- they do not manufacture any products under the names of LEDSO or DAKAVIR
- they do not manufacture Daclatasvir 60mg at this moment in time.

No serious adverse reactions attributed to these falsified products have been reported at this stage.


### Swissmedic warns about falsified Harvoni® packs

Switzerland – The Swiss Agency for Therapeutic Products Swissmedic has warned that falsified packs of the hepatitis C medicine Harvoni® have been discovered in Israel. The plastic bottles, which originate in India, were imported via a Swiss trading company and contain white instead of genuine yellow film-coated tablets. Swissmedic is working with other European authorities to establish whether falsified Harvoni® packs have also been imported into other countries.

► Swissmedic Announcement, 4 March 2016.
Regulatory news

**Medicines regulation**

**New biosimilar regulations in Australia**

Australia – The TGA has published version 2.0 of its biosimilar regulations. A new section has been added on adverse event reporting requirements, including the information that should be provided to identify the biosimilar linked to each incident, namely: its brand identity, its non-proprietary name (i.e. the Australian biological name), its AUST R and batch numbers, and its expiration date and dosage form.

The new guidance also defines the data requirements for registration of new biosimilars in terms of laboratory and clinical studies demonstrating their comparability (biosimilarity) to the reference biological medicine already registered in Australia. The guidance further states when and how companies can compare their biosimilars to products that are not registered in Australia.

The new version of the regulations is largely based on EMA guidance documents.

► Asia Regulatory Roundup, 22 December 2015.


**EMA launches PRIME scheme for medicines targeting unmet needs**

European Union – The EMA has launched its new PRIME (PRIority MEdicines) scheme to accelerate access to medicines that offer a major therapeutic advantage over existing treatments, or benefit patients with no treatment options. Through PRIME, EMA offers early, proactive and enhanced support to medicine developers to optimize the generation of robust data on a medicine’s benefits and risks and enable accelerated assessment of medicine applications.

PRIME builds on the existing regulatory framework and available tools. This means that a PRIME medicine is expected to benefit from accelerated assessment at the time of an application for marketing authorization. To be accepted for PRIME, a medicine has to show its potential to benefit patients with unmet medical needs based on early clinical data. While PRIME is open to all companies, micro-, small- and medium-sized enterprises (SMEs) and applicants from the academic sector can apply earlier on the basis of compelling non-clinical data and tolerability data from initial clinical trials.

► EMA Press release, 7 March 2016.

**EMA guidance for industry on clinical studies and clinical data publication**

European Union – The European Medicines Agency (EMA) has informed applicants for centralized marketing authorization that if a pivotal clinical study is found to be non-compliant with good clinical practice (GCP) during the assessment, it cannot be replaced by another study. A new application must be submitted which is supported by appropriate GCP-compliant data from a
Safety features on packaging to be introduced in Europe

European Union – Following the approval of a new regulation of the Falsified Medicines Directive the EMA and the European Commission have published an implementation plan to guide applicants and marketing-authorization holders in meeting the new requirements.

The Delegated Regulation introduces two safety features – a unique identifier (a two-dimension barcode) and an anti-tampering device – to be placed on the packaging of most medicines for human use. Marketing authorization holders are required to place the safety features on the packaging of most prescription medicines and certain non-prescription medicines no later than 9 February 2019.


International Health Regulations

Poliovirus spread: continued public health emergency

Geneva – The International Health Regulations (IHR) Emergency Committee unanimously agreed that the international spread of polio remains a Public Health Emergency of International Concern and recommended the extension of the temporary recommendations for a further three months. The recommendations essentially aim to ensure vaccine coverage to eradicate polio globally, including in vulnerable areas.

► WHO Statement, 1 March 2016.

EMAs pivotal study. With this position the EMA aims to reinforce the application of GCP during the conduct of clinical trials. (1)

The EMA has also issued guidance for pharmaceutical companies to operationalize its new policy on proactive publication of clinical data, which entered into force on 1 January 2015. The guidance includes recommendations on how to anonymize clinical reports and how identify and redact commercially confidential information. (2)

► (1) EMA News, 30 November 2015.
(2) EMA News, 3 March 2015.

EMA increases access to reports on adverse reactions

European Union – The EMA has adopted a revised access policy for its EudraVigilance database, which holds the reports of suspected adverse reactions to medicines authorized in the European Economic Area (EEA).

Under the revised policy, the Uppsala Monitoring Centre (UMC) of WHO will be provided with individual case safety reports originating from within the EEA on a daily basis in accordance with a data transfer agreement concluded in December 2015. Medicines regulatory authorities in countries outside the EEA can obtain data in line with the WHO dataset upon request. Academia can obtain extended access to data sets for specific research activities, and marketing authorization holders will be given enhanced access to reports on their medicines in support of their pharmacovigilance obligations.

The changes will come into effect in the third quarter of 2017 together with a series of technical improvements to the EudraVigilance system.

► EMA Press release, 18 December 2015
Zika virus disease a public health emergency
Geneva – On 1st February 2016 the WHO Director-General declared a Public Health Emergency of International Concern related to the recent increase of Zika virus infection in Brazil. The concern relates to the increased number of infants born with microencephaly and of other neurologic disorders observed in Brazil in connection with the spread of the virus during 2015. A similar cluster was observed in French Polynesia in 2014.

The Emergency Committee convened under the International Health Regulations (2005) has recommended that aggressive measures should be taken to reduce the risk of infection with Zika virus, particularly among women of childbearing age. No travel or trade restrictions have been recommended. In the longer term, research and development will be intensified for Zika virus vaccines, therapeutics and diagnostics. (1)

European Union – In response to the WHO announcement, the EMA has set up a task force to provide advice on any scientific and regulatory matters for the research and development of medicines or vaccines against the Zika virus. (2)

The International Coalition of Medicines Regulatory Authorities (ICMRA) has pledged its support to WHO in countering the Zika outbreak (3). ICMRA brings together 21 medicines regulators from every region in the world. Its members are working together to fight against Zika virus disease, building on ICMRA’s collaborative work on Ebola.

► (1) WHO statement, 1 February 2016. (2) EMA News, 8 February 2016. (3) MHRA Announcement, 10 February 2016, and announcements on the web sites of other participating regulatory authorities.

Blood safety

FDA updates blood donor deferral policies
United States of America – The FDA has provided guidance on blood donor deferral to reduce the risk of human immunodeficiency virus (HIV) transmission and Zika virus transmission.

To reduce the risk of HIV transmission, men who have sex with men will be deferred for 12 months since the last sexual contact with another man, instead of indefinitely. This deferral period is more aligned with that recommended for other at-risk individuals and that recommended in other countries (1).

To reduce the risk of Zika virus transmission the FDA has recommended that donors at risk for Zika virus infection be deferred for four weeks if they have had symptoms suggestive of Zika virus infection or have potentially been exposed to the virus by travelling to an area with active Zika virus transmission or through sexual contact. The FDA recommends that whole blood and blood components for transfusion be obtained from areas without active transmission. (2)

The FDA has also issued new recommendations to reduce the risk of Zika virus transmission from human cells, tissues and cellular and tissue-based products, for immediate implementation. (3)

**Approved**

**Sebelipase alfa for lysosomal acid lipase (LAL) deficiency**

**Product name:** Kanuma®

**Dosage form:** Concentrate for solution for intravenous infusion

**Class:** rhLAL protein, enzyme;  
**ATC code:** A16AB14

**Approval:** FDA (orphan drug; breakthrough therapy)

**Use:** Treatment of patients with LAL deficiency, also known as Wolman disease and as cholesteryl ester storage disease (CESD). LAL deficiency is a rare inherited genetic disorder that can lead to serious and life-threatening organ damage.

**Benefits:** Increased survival of infants with rapidly progressing Wolman disease at 12 months of age; improvement in disease-related parameters in CESD patients.

**Notes:** The product is produced in the egg whites of genetically engineered chickens. The U.S. Center for Veterinary Medicine (CVM) determined that the rDNA construct is safe for the animals and is stable in the genome of the chicken over several generations. Neither the chicken nor the eggs are allowed in the food supply. The product was approved in the EU in August 2015.

► FDA News release, 8 December 2015.

**Albutreponacog alfa for Haemophilia B**

**Product name:** Idelvion®

**Dosage form:** Powder and solvent for solution for injection

**Class:** Antihaemorrhagic, blood coagulation factor IX;  
**ATC code:** B02BD04

**Approval:** FDA (non-proprietary name: Coagulation factor IX (recombinant), albumin fusion protein); EMA (orphan designation)

**Use:** Treatment and prophylaxis of bleeding in patients with Haemophilia B

**Benefits:** Ability to stop and prevent bleeding.

FDA News release, 4 March 2016.

**Recombinant von Willebrand factor for control of bleeding episodes**

**Product name:** Vonvendi®

**Dosage form:** Lyophilized powder for solution for intravenous injection

**Class:** Blood coagulation factor; recombinant von Willebrand factor (first-in-class approved by FDA);  
**ATC code:** B02BD10

**Approval:** FDA (orphan product designation)

**Use:** On-demand (as needed) treatment and control of bleeding episodes in adults diagnosed with von Willebrand disease

**Benefits:** Additional therapeutic option for the treatment of bleeding episodes in patients with von Willebrand disease

► FDA News release, 8 December 2015.

**Selexipag for pulmonary arterial hypertension**

**Product name:** Utravi®

**Dosage form:** Tablets

**Class:** Oral IP prostacyclin receptor agonist;  
**ATC code:** B01AC27

**Approval:** FDA (orphan drug designation); EMA (orphan medicinal product designation)

**Use:** Treatment of adults with pulmonary arterial hypertension

**Benefits:** Ability to decrease the elevated pressure in the vessels supplying blood to the lungs.

► FDA News release, 8 December 2015.  
EMA Summary of opinion, 28 January 2016.
**Emtricitabine/tenofovir alafenamide for HIV infection**

**Product name:** Descovy®

**Dosage form:** Film-coated tablets

**Class:** Fixed-dose combination of two antiretrovirals, reverse transcriptase inhibitors; **ATC code:** J05AR17

**Approval:** EMA

**Use:** In combination with other antiretroviral agents, for the treatment of adults and adolescents infected with human immunodeficiency (HIV) virus type 1

**Benefits:** Lower impact on renal safety and bone mineral density compared with tenofovir disoproxil-containing regimens.


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**Emtricitabine/rilpivirine/tenofovir alafenamide for HIV infection**

**Product name:** Odefsey®

**Dosage form:** Tablets

**Class:** Fixed dose combination of three antiretrovirals; **ATC code:** J05AR19

**Approval:** FDA

**Use:** Complete treatment regimen for HIV-1 infection in patients from 12 years of age as initial therapy in ARV treatment-naïve patients with ≤100 000 RNA copies per mL; or to replace a stable antiretroviral regimen in patients with less than 50 RNA copies per mL for at least six months, no history of treatment failure and no known substitutions associated with resistance to the individual drug components.

**Benefits:** Lower impact on renal safety and bone mineral density compared with tenofovir disoproxil-containing regimens.


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**Uridine triacetate for emergency treatment of chemotherapy overdose**

**Product name:** Vistogard®

**Dosage form:** Oral granules

**Class:** Pyrimidine analogue

(at **ATC code:** L01BC)

**Approval:** FDA

**Use:** Emergency treatment of overdose or life-threatening toxicity of fluorouracil or capecitabine

**Benefits:** First-of-its-kind therapy that can block cell damage and cell death caused fluorouracil by competitive inhibition.

**Notes:** The safety and efficacy of uridine triacetate initiated more than 96 hours following the end of treatment with fluorouracil or capecitabine have not been established. Uridine triacetate is not recommended for treating non-emergency adverse reactions associated with fluorouracil or capecitabine because it may lessen the efficacy of these drugs.

► FDA News release, 11 December 2015.
Elotuzumab for multiple myeloma
Product name: Empliciti®
Dosage form: Concentrate for solution for infusion
Class: Monoclonal antibody; ATC code (temporary): L01XC23
Approval: EMA (orphan designation)
Use: In combination with lenalidomide and dexamethasone, treatment of multiple myeloma in patients who have received at least one prior therapy
Benefits: Ability to delay the progression of disease and to increase the proportion of patients who have a response.

Alectinib for certain advanced non-small cell lung cancers
Product name: Alecensa®
Dosage form: Capsules
Class: ALK (anaplastic lymphoma kinase) blocker; ATC code (temporary): L01XE36
Approval: FDA (accelerated approval; breakthrough therapy designation, priority review status; orphan drug designation)
Use: Treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer who progressed on, or are intolerant to, crizotinib.
Benefits: New therapy for certain types of advanced metastatic non-small cell lung cancer, with ability to reduce primary tumours in the lung and brain metastases.
Safety information: Serious side effects include hepatotoxicity, interstitial lung disease, bradycardia and severe myalgia. Women treated with alectinib should use effective contraception. Patients treated with alectinib should avoid sun exposure and use a broad spectrum sunscreen.
► FDA News release, 11 December 2015.

Lesinurad for hyperuricaemia
Product name: Zurampic®
Dosage form: Film-coated tablets
Class: Selective reabsorption inhibitor of uric acid transporter 1 (URAT1);
ATC code: M04AB05
Approval: EMA, FDA
Use: Adjunctive treatment of hyperuricaemia in combination with a xanthine oxidase inhibitor in adults with gout.
Benefits: Ability to increase uric acid excretion and thereby lower serum uric acid levels.
► EMA/CHMP Summary of opinion, 17 December 2015.
FDA News release, 22 December 2015.

Brivaracetam for epilepsy
Product name: Briviact®
Dosage form: Tablets, oral solution, and solution for injection/infusion
Class: Antiepileptic; ATC code: N03AX23
Approval: FDA, EMA
Use: Adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients from 16 years of age with epilepsy
Benefits: Ability to reduce the frequency of partial-onset epileptic seizures.
► FDA News release, 19 February 2016.
EMA/CHMP Summary of opinion, 19 November 2015.

“Follow-on” biological product
Insulin glargine
Product name: Basaglar®
Dosage form: Injection
Class: Long-acting human insulin analog
Approval: FDA final approval
Use: Improvement of glycaemic control in adults and paediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus
Note: Basaglar® is the first insulin product approved through an abbreviated approval
Approved pathway under the Federal Food, Drug, and Cosmetic Act. A 505(b)(2). The application submitted for its marketing authorization relied, in part, on the FDA’s finding of safety and effectiveness for Lantus® (insulin glargine injection), and demonstrated that Basaglar® was sufficiently similar to Lantus® to scientifically justify such reliance.

Basaglar® was not approved as a biosimilar product, as there was no insulin glargine “reference product” licensed under the Public Health Service Act.

► FDA News release, 16 December 2015.

Extensions of indications

Nivolumab for kidney cancer
Product name: Opdivo®
Approval: EMA
Newly approved use: Treatment of adult patients with advanced renal cell carcinoma.
(See also the Safety news on page 49)

Eribulin for liposarcoma
Product name: Halaven®
Approval: FDA (orphan drug designation, priority review)
Newly approved use: Treatment of unresectable or metastatic liposarcoma in patients who received prior chemotherapy containing an anthracycline drug.
Publications and events

**Development**

**WHO report on health development goals**

Geneva – WHO has launched its report *Health in 2015: from MDGs to SDGs*, which looks at results achieved since 2000 against the health millennium development goals (MDGs) and identifies priorities for the key areas outlined in the health-related sustainable development goals (SDGs) in the next 15 years.

Key ingredients for success in the past 15 years included a doubling in global funding for health, the creation of new funding mechanisms and partnerships, and the critical role of civil society in tackling diseases.

Universal health coverage is the linchpin underlying the new, inclusive focus in the new sustainable development agenda. A new focus will lie on preventing and treating non-communicable diseases. The report includes the latest data on health trends and explores how global health is linked to the other 16 SDGs and to emerging issues such as technological and environmental change.

Better health data systems will be crucial to measure and evaluate progress. The WHO *Global Reference List of 100 Core Health Indicators*, published in 2015, is a first step towards the Health Data Collaborative that WHO is working to establish with global partners in 2016.


**Access to health products**

**MPP signs licensing agreements**

Geneva – In December 2015 the Medicines Patent Pool (MPP) signed a new licensing agreement with AbbVie to help ensure sustainability of long-term supply of lopinavir/ritonavir (LPV/r), the most widely used second-line HIV treatment in South Africa and across Africa. Generic manufacturers with stringent regulatory approval that obtain a licence from the MPP will be able to manufacture and sell generic versions of LPV/r, as well as combinations of ritonavir with other ARVs, throughout Africa. The agreement has been actively encouraged by the South African government. In December 2014 an agreement had been signed with AbbVie for paediatric formulations of LPV/r. *(1)*

In January 2016 the MPP signed its first round of sub-licences for the hepatitis C medicine daclatasvir developed by Bristol-Myers Squibb, enabling the generic companies Cipla, Emcure, Hetero and Natco to produce and sell daclatasvir in 112 low- and middle-income countries. Under the licence, the generic manufacturers can develop fixed-dose combinations that offer the potential to treat all six major genotypes of the hepatitis C virus. MPP expects to grant further sub-licences soon. *(2)*

► *(1)* [MPP Announcement, 18 December 2015](http://www.medicines-pool.org/).

► *(2)* [MPP Announcement, 20 January 2016](http://www.medicines-pool.org/).
Call for applications for the 2017 WHO Model EML and EMLc

Geneva – WHO has called for applications seeking inclusion, changes to or removal of medicines on the WHO Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc). The application period has been extended until 2 December 2016 to facilitate interaction between applicants and the EML Secretariat to ensure that applications adequately address the critical elements for selection: public health relevance, clinical efficacy and safety of the proposed medicine. The WHO Expert Committee on Selection and Use of Essential Medicines will meet in April 2017.


Impact factor of key medicines

A paper published in PLoS ONE proposes a model measuring the impact of key malaria, tuberculosis and HIV/AIDS medicines on global health in terms of averting loss of disability-adjusted life-years. The study suggests that key drugs for these three diseases are, together, ameliorating about 37% of the global burden of the three diseases. Artemether/lumefantrine and artesunate/amodiaquine have the greatest impact globally across the three diseases, followed by lamivudine and four first-line tuberculosis drugs. Drug impacts vary widely across countries depending on disease patterns and access to medicines.

This index provides useful information for policy makers, pharmaceutical companies, countries, and other stakeholders working to increase access to essential medicines.


The Global Health Impact. Web site. global-health-impact.org

Making medicines in Africa

A new book titled Making medicines in Africa - The political economy of industrializing for local health looks at the industrial development of pharmaceutical production in Sub-Saharan Africa, and at how the capabilities that it generates can help the subcontinent to tackle its health care needs by improving access to good quality essential medicines.

The book presents original research, much of it from recent fieldwork in African contexts. The authors include academics, researchers and practitioners, some of whom have been or are currently managing pharmaceutical firms in African contexts while others are involved in policy formulation and implementation.


WHO to fast-track availability of Zika diagnostics

Geneva – The Department of Essential Medicines and Health Products has issued an expression of interest call to manufactures and product development partnerships who have developed in vitro diagnostic tests for Zika virus disease. Interested parties can submit their products to WHO for assessment through the Emergency Assessment and Listing (EUAL) procedure, designed during the Ebola outbreak. This procedure serves
to evaluate products during public health emergencies of international concern. In parallel WHO is working on establishing regulatory support to accelerate assessment and approval of future clinical trials for potential vaccines and treatments for Zika virus disease.

WHO In vitro diagnostics and laboratory technology. EUAL Procedure for Zika Virus Disease (IVDs) [web page].

Diseases

Top emerging pathogens
Geneva – A panel of scientists and public health experts convened by WHO have identified the top emerging pathogens likely to cause severe outbreaks in the near future, and for which few or no medical countermeasures exist. These include: Crimean Congo haemorrhagic fever, Ebola virus disease and Marburg, Lassa fever, MERS and SARS coronavirus diseases, Nipah and Rift Valley fever. These infections need urgent research and development (R&D) attention and other measures to increase preparedness. Three other diseases were designated as “serious”, requiring action as soon as possible, namely: chikungunya, severe fever with thrombocytopenia syndrome, and Zika.

HIV/AIDS, tuberculosis, malaria, avian influenza, dengue and some other diseases with epidemic potential were not included in the list because major disease control and research networks and a pipeline for improved interventions are in place to combat these infections.

The list will be reviewed annually or when new diseases emerge.

Ebola: transmission chains stopped but new flare-ups likely
Geneva – WHO has declared the end of the most recent outbreak of Ebola virus disease in Liberia. While all known chains of transmission have been stopped in West Africa, the Organization warns that more flare-ups are expected and that strong surveillance and response systems will be critical in the months to come. A massive effort is under way to ensure robust prevention, surveillance and response capacity across the three hardest-hit countries – Guinea, Liberia and Sierra Leone – by the end of March.

Malaria: more countries moving towards elimination
Brussels – New estimates from WHO show a significant increase in the number of countries moving towards malaria elimination. According to the World Malaria Report 2015, an estimated 6.2 million deaths have been averted since 2000, and an estimated US$ 900 million in case management costs have been saved in Africa in that period. Insecticide-treated mosquito nets contributed the largest savings, followed by artemisinin-based combination therapies and indoor residual spraying. The use of rapid diagnostic tests has increased sharply and has enabled timely and appropriate treatment.

However, about 3.2 billion people – nearly half of the world’s population – remain at risk of malaria globally. Fifteen
countries, mainly in Africa, account for 80% of global malaria cases. New challenges have emerged, notably the increasing resistance of mosquitoes to insecticides and of Plasmodium parasites to medicines.

In May 2015, the World Health Assembly adopted the WHO “Global Technical Strategy for Malaria 2016-2030”, a new 15-year framework for malaria control in all endemic countries. Achieving its targets will require country leadership, sustained political commitment and a tripling of current annual funding to US$ 8.7 billion by 2030.

► WHO News release, 9 December 2015.

Rabies: new global framework launched

Geneva – A new framework to eliminate human rabies has been launched by WHO, the World Organization for Animal Health (OIE), the Food and Agriculture Organization of the United Nations (FAO) and the Global Alliance for the Control of Rabies (GARC).

The framework calls for three key actions: making human vaccines and antibodies affordable, ensuring prompt treatment of people who get bitten, and mass dog vaccinations to tackle the disease at its source.

Tens of thousands of people, many of them children, die from rabies each year. About 80% of people exposed to rabies live in poor, rural areas of Africa and Asia.

► WHO News release, 10 December 2015.

Antibiotics

Industry declaration on combating antimicrobial resistance

Davos – In a declaration signed at the 2016 annual World Economic Forum in Davos, Switzerland, more than 80 international pharmaceutical, generics, diagnostics and biotechnology companies, as well as key industry bodies, have outlined their views on how industry and governments should work together to combat the threat of antimicrobial resistance. They called for more predictable and sustainable markets with incentives for research and development of antibiotics, and committed to action to help reduce the development of drug resistance, increase R&D investment meeting global public health needs, and improve equitable access to high quality antibiotics.

In her comments the WHO Director-General said that WHO and its Member States have called for the development of new antimicrobial medicines and affordable access to them in line with the global action plan on antimicrobial resistance, and that the Declaration affirms that the challenges of antimicrobial resistance can be addressed only through collaboration and global collective action.

Consultation documents

To receive draft monographs by email please contact Mrs Wendy Bonny (bonnyw@who.int), specifying that you wish to be added to the electronic mailing list.

The International Pharmacopoeia

Misoprostol
(Misoprostolum)

This is a revised draft proposal for The International Pharmacopoeia (Working document QAS/15.602/Rev.1, November 2015).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

[Note from the Secretariat. The following monograph is proposed for inclusion in The International Pharmacopoeia.]

Molecular formula. \(C_{22}H_{38}O_{5}\)

Relative molecular mass. 382.5

Graphic formula

its epimer at \(C^*\) and their enantiomers

Chemical name
Mixture of methyl rac-7-\{1R,2R,3R\}-3-hydroxy-2-\{(1E,4R)-4-hydroxy-4-methyloct-1-en-1-yl\}-5-oxocyclopentyl\)heptanoate and methyl rac-7-\{1R,2R,3R\}-3-hydroxy-2-\{(1E,4S)-4-hydroxy-4-methyloct-1-en-1-yl\}-5-oxocyclopentyl\)heptanoate; CAS Reg. No. 59122-46-2.

Description. Clear, colourless or yellowish, oily liquid.

Solubility. Practically insoluble in water R, soluble in dehydrated ethanol R, sparingly soluble in acetonitrile R.
Category. Prostaglandin (PGE₁) analogue.

Storage. Misoprostol neat oil should be kept in a tightly sealed container and stored at a temperature between -25 and -10°C.

Additional information. Misoprostol is hygroscopic. It is gradually degraded at room temperature, the degradation being faster at higher temperatures.

Requirements

Definition. Misoprostol contains not less than 96.5% and not more than 102.0% of \( \text{C}_{22}\text{H}_{38}\text{O}_{5} \) with reference to the anhydrous substance.

Identity tests

Either test A or tests B and C may be applied.

A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from misoprostol RS or with the reference spectrum of misoprostol.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R3 as the coating substance and a mixture of 8 volumes of toluene R, 2 volumes of ethyl acetate R, 1 volume of dehydrated ethanol R and 0.1 volume of glacial acetic acid R as the mobile phase, prepared immediately before use. Apply separately to the plate 100 μL of each of the following two solutions in dehydrated ethanol R. For solution (1) use 0.1 mg of the test substance per mL. For solution (2) use 0.1 mg of misoprostol RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air, expose it to the vapour of iodine R and examine the chromatogram in daylight.

The principal spot obtained with solution (1) corresponds in position, appearance and intensity to that obtained with solution (2).

C. Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (15 cm × 4.6 mm) packed with octadecylsilyl silica gel (5 μm).¹

Use the following conditions for gradient elution:

- Mobile phase A: mix 28 volumes of acetonitrile for chromatography R with 69 volumes of water R and 3 volumes of methanol R;
- Mobile phase B: mix 47 volumes of acetonitrile for chromatography R with 50 volumes of water R and 3 volumes of methanol R.

¹ An Ascentis Express C18 column was found suitable.
Maintain the column temperature at 35°C.

Prepare the following solutions using a mixture of 31 volumes of acetonitrile R and 69 volumes of water R as solvent. For solution (1) dissolve about 50 mg of the test substance in 10.0 mL and sonicate for about 10 minutes. Ensure that the temperature of the sonication bath is below room temperature to avoid degradation of misoprostol. For solution (2) dilute 1 volume of solution (1) to 500 volumes. For solution (3) heat 5 mL of solution (1) in a water bath at 75°C for 1 hour.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 200 nm. Store the samples at 4°C during analysis using a cooled autosampler.

Inject 20 µL of solution (3). The test is not valid unless the peak-to-valley ratio (Hp/Hv) is at least 5.0, where Hp is the height above the extrapolated baseline of the peak due to impurity A (with a relative retention of about 0.95 with reference to misoprostol (retention time about 21 minutes)) and Hv is the height above the extrapolated baseline at the lowest point of the curve separating the peak due to impurity A from the peak due to misoprostol.

Inject alternately 20 µL each of solutions (1) and (2).

The chromatogram obtained with solution (1) may show the following impurities at the following relative retentions with reference to misoprostol (retention time about 21 minutes): impurity E (1st peak): about 0.84; impurity E (2nd peak): about 0.86; impurity B (1st peak): about 0.90; impurity B (2nd peak): about 0.92; impurity A: about 0.95; impurity D: about 1.27; impurity C: about 1.37. Use also the chromatogram obtained with solution (3) to identify impurity A and C.

In the chromatogram obtained with solution (1):

• the sum of the areas of any peak corresponding to impurity A, B and E is not greater than 7.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);
• the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.76, is not greater than 0.75 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);
• the area of any other impurity peak is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);
• the sum of the corrected area of any peak corresponding to impurity C and the areas of all other peaks, other than the principal peak, is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%). Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comment</th>
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<tr>
<td>0–5</td>
<td>100</td>
<td>0</td>
<td>isocratic</td>
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<tr>
<td>5–15</td>
<td>100 to 65</td>
<td>0 to 35</td>
<td>linear gradient</td>
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<td>15–22</td>
<td>65</td>
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<td>22–25</td>
<td>65 to 0</td>
<td>35 to 100</td>
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<td>0 to 100</td>
<td>100 to 0</td>
<td>linear gradient</td>
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<td>32–40</td>
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<td>0</td>
<td>re-equilibration</td>
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</table>
Diastereoisomers
Carry out the test as described under 1.14.4 High performance liquid chromatography using a stainless steel column (15 cm × 2.1 mm) packed with silica gel for chromatography R (3.5 μm). As the mobile phase use a mixture of 4 volumes of 2-propanol R, 96 volumes of heptane R and 0.1 volume of trifluoroacetic acid R.

As the test solution use 1.0 mg of the test substance per mL of a mixture of 4 volumes of 2-propanol R and 96 volumes of heptane R.

Maintain the column temperature at 25°C.

Operate with a flow rate of 0.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 205 nm. Store the samples at 4°C during analysis using a cooled autosampler.

Inject 10 μL of the test solution.

The chromatogram shows two principal peaks due to misoprostol at retention times of about 14 and 16 minutes. The test is not valid unless the resolution between these two peaks is at least 2.0.

Measure the areas of the two peaks corresponding to misoprostol. The first peak of misoprostol is 45%–55% of the sum of the areas of the two peaks due to misoprostol.

Assay
Carry out the test as described under 1.14.4 High performance liquid chromatography using a stainless steel column (15 cm × 4.6 mm) packed with octadecylsilyl silica gel (5 μm). As the mobile phase use a mixture of 45 volumes of acetonitrile R and 55 volumes of water.

Prepare the following solutions in the mobile phase. For solution (1) use 0.1 mg of misoprostol per mL. For solution (2) use 0.1 mg of misoprostol RS per mL.

Maintain the column temperature at 35°C.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 200 nm. Store the samples at 4°C during analysis using a cooled autosampler.

Inject alternately 20 μL each of solutions (1) and (2). The test is not valid unless the symmetry factor of the peak due to misoprostol is between 0.8 and 1.5.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of misoprostol (C₂₂H₃₈O₅), using the declared content of C₂₂H₃₈O₅ in misoprostol RS.

Impurities

A. Mixture of methyl rac-7-[(1R,2S,3S)-3-hydroxy-2-[(1E,4R)-4-hydroxy-4-methyloct-1-en-1-yl]-5-oxocyclopentyl]heptanoate and methyl rac-7-[(1R,2S,3S)-3-hydroxy-2-[(1E,4S)-4-hydroxy-4-methyloct-1-en-1-yl]-5-oxocyclopentyl]heptanoate (8-epimisoprostol)

2 An Xbridge HILIC column was found suitable.
3 An Ascentis Express C18 column was found suitable.
B. Mixture of methyl 7-[(1RS,2SR,3RS)-3-hydroxy-2-[(1E,4RS)-4-hydroxy-4-methylct-1-enyl]-5-oxocyclopentyl]heptanoate and methyl 7-[(1RS,2SR,3RS)-3-hydroxy-2-[(1E,4SR)-4-hydroxy-4-methylct-1-enyl]-5-oxocyclopentyl]heptanoate (12-epimisoprostol) (synthesis impurity).

C. Mixture of methyl rac-7-[(1R,2S)-2-[(1E,4R)-4-hydroxy-4-methylct-1-en-1-yl]-5-oxocyclopent-3-en-1-yl]heptanoate and methyl rac-7-[(1R,2S)-2-[(1E,4S)-4-hydroxy-4-methylct-1-en-1-yl]-5-oxocyclopentyl]heptanoate. (misoprostol A)

D. Methyl rac-7-2-[(1E,4R)-4-hydroxy-4-methylct-1-en-1-yl]-5-oxocyclopent-1-en-1-yl}heptanoate (misoprostol B)

E. (+) - methyl (1R,2R,3R)-3-hydroxy-2-[(1E,4RS)-(1,5-heptadien-1-yl)]-4-hydroxy-4,6-dimethyl-5-oxocyclopentaneheptanoate

[Note from the Secretariat. Chemical name to be confirmed.]
Misoprostol dispersion  
*(Misoprostoli dispersio)*

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.642, November 2015).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

[Note from the Secretariat. The following monograph is proposed for inclusion in The International Pharmacopoeia. Comments are in particular sought on the suitability of the proposed content limits for misoprostol (95.0% to 105.0% of the amount of Misoprostol stated on the label).]

**Description.** A white or almost white powder.

**Category.** Prostaglandin (PGE₁) analogue.

**Storage.** Misoprostol is hygroscopic, it should be stored below 8°C under nitrogen in sealed containers and should not be exposed to moisture.

**Requirements**

**Definition.** Misoprostol dispersion is a mixture of Misoprostol and Hypromellose. It contains not less than 95.0% and not more than 105.0% of the amount of C₂₂H₃₈O₅ stated on the label.

**Identity tests**

Either tests A and C or tests B and C may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”. The retention time of the principal peak in the chromatogram obtained from solution (1) corresponds to the retention time of the peak due to misoprostol in the chromatogram obtained from solution (2).

B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R3 as the coating substance and a mixture of 8 volumes of toluene R, 2 volumes of ethyl acetate R, 1 volume of dehydrated ethanol R and 0.1 volume of glacial acetic acid R as the mobile phase, prepared immediately before use. Apply separately to the plate 100 μL of each of the following two solutions in dehydrated ethanol R. For solution (1) shake mechanically a quantity of the dispersion equivalent to 1 mg of misoprostol with 10.0 mL of dehydrated ethanol R for 10 minutes, filter and use the clear filtrate. For solution (2) use 0.1 mg of misoprostol RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air, expose it to the vapour of iodine R and examine the chromatogram in daylight.

The principal spot obtained with solution (1) corresponds in position, appearance and intensity to that obtained with solution (2).

C. Carry out test C1, C2 and C3.
C1. Add gently 1 g of the dispersion to 100 mL of water in a beaker. Allow the substance to disperse over the surface, tapping the top of the container to ensure an even dispersion of the substance. Allow the beaker to stand for about 5 hours until the substance becomes transparent and mucilaginous. Swirl the beaker to wet the remaining substance. Add a stirring bar and stir until the test substance is completely dissolved. To two 50 mL aliquots of this solution add an equal volume of either sodium hydroxide (~40 g/L) TS or hydrochloric acid (~36.5 g/L) TS. Both mixtures remain stable and clear.

C2. Add 1 g of the dispersion to 100 mL of boiling water and stir the mixture; a slurry is formed but the dispersion does not dissolve. Cool the slurry to 20°C and stir. The resulting liquid is clear or an opalescent, mucilaginous colloidal mixture.

C3. Pour a few mL of the mixture prepared for identity test C2 onto a glass plate and allow the water to evaporate. A thin, self-sustaining film is formed.

Loss on drying. Dry at 105°C for 2 hours; it loses not more than 50 mg/g.

Related substances
Prepare fresh solutions and perform the tests without delay.

Carry out the test as described under 1.14.4 High performance liquid chromatography using a stainless steel column (15 cm × 4.6 mm) packed with octadecylsilyl silica gel (5 μm).¹

Use the following conditions for gradient elution:

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–5</td>
<td>100</td>
<td>0</td>
<td>isocratic</td>
</tr>
<tr>
<td>5–15</td>
<td>100 to 65</td>
<td>0 to 35</td>
<td>linear gradient</td>
</tr>
<tr>
<td>15–22</td>
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<td>22–25</td>
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</tr>
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<td>30–32</td>
<td>0 to 100</td>
<td>100 to 0</td>
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</tr>
<tr>
<td>32–40</td>
<td>100</td>
<td>0</td>
<td>re-equilibration</td>
</tr>
</tbody>
</table>

Maintain the column temperature at 35°C.

Prepare the following solutions using a mixture of 31 volumes of acetonitrile R and 69 volumes of water as solvent. For solution (1) mix a quantity of the dispersion equivalent to about 8 mg of misoprostol, accurately weighed, with 20.0 mL of acetonitrile R and sonicate for 10 minutes. Ensure that the temperature of the sonication bath is below room temperature to avoid degradation of misoprostol. Centrifuge and filter the supernatant. Evaporate 8.0 mL of the filtrate to dryness with nitrogen, dissolve the residue in 4.0 mL of solvent, using a vortex mixer. For solution (2) dilute 1 volume of solution (1) to 500 volumes. For solution (3) heat 2 mL of solution (1) in a water bath at 75°C for 1 hour.

¹ An Ascentis Express C18 column was found suitable.
Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 200 nm. Store the samples at 4°C during analysis, using a cooled autosampler.

Inject 100 µL of solution (3). The test is not valid unless the peak-to-valley ratio (Hp/Hv) is at least 5.0, where Hp is the height above the extrapolated baseline of the peak due to impurity A (with a relative retention of about 0.95 with reference to misoprostol (retention time about 21 minutes) and Hv is the height above the extrapolated baseline at the lowest point of the curve separating the peak due to impurity A from the peak due to misoprostol.

Inject alternately 100 µL each of solutions (1) and (2).

The chromatogram obtained with solution (1) may show the following impurities at the following relative retentions with reference to misoprostol (retention time about 21 minutes): impurity E (1st peak): about 0.84; impurity E (2nd peak): about 0.86; impurity B (1st peak): about 0.90; impurity B (2nd peak): about 0.92; impurity A: about 0.95; impurity D: about 1.27; impurity C: about 1.37. Use also the chromatogram obtained with solution (3) to identify impurity A and C.

In the chromatogram obtained with solution (1):

• the sum of the areas of any peak corresponding to impurity A, B and E is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);

• the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.76, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

• the area of any other impurity peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

• the sum of the corrected area of any peak corresponding to impurity C and the areas of all other peaks, other than the principal peak, is not greater than 12.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%). Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Diastereoisomers

Carry out the test as described under 1.14.4 High performance liquid chromatography using a stainless steel column (15 cm × 2.1 mm) packed with silica gel for chromatography R (3.5 µm). As the mobile phase use a mixture of 4 volumes of 2-propanol R, 96 volumes of heptane R and 0.1 volume of trifluoroacetic acid R.

Prepare the following test solution using as a solvent a mixture of 4 volumes of 2-propanol R and 96 volumes of heptane R. Mix a quantity of the dispersion equivalent to about 2 mg of misoprostol with 5.0 mL of acetonitrile R and sonicate for 10 minutes ensuring that the temperature of the sonication bath is below room temperature to avoid degradation of misoprostol. Centrifuge and filter the supernatant. Evaporate 2.0 mL of the filtrate to dryness with nitrogen, dissolve the residue in 1.0 mL of solvent and vortex for 1 min.

Maintain the column temperature at 25°C.

Operate with a flow rate of 0.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 205 nm. Store the samples at 4°C during analysis, using a cooled autosampler.

2 An Xbridge HILIC column was found suitable.
Inject 10 µL of the test solution.

The chromatogram shows two principal peaks due to misoprostol at retention times of about 14 and 16 minutes. The test is not valid unless the resolution between these two peaks is at least 2.0.

Measure the areas of the two peaks corresponding to misoprostol. The first peak of misoprostol is 45% to 55% of the sum of the areas of the two peaks due to misoprostol.

**Assay**

Carry out the test as described under 1.14.4 High performance liquid chromatography using a stainless steel column (15 cm × 4.6 mm) packed with octadecylsilyl silica gel (5 µm).\(^3\) As the mobile phase use a mixture of 45 volumes of acetonitrile R and 55 volumes of water.

Prepare the following solutions in the mobile phase. For solution (1) mix a quantity of the dispersion equivalent to about 4 mg of misoprostol, accurately weighed, with 200.0 mL of mobile phase and sonicate for 10 minutes. Ensure that the temperature of the sonication bath is below room temperature to avoid degradation of misoprostol. Filter a portion of this solution, discarding the first few mL of the filtrate. For solution (B) use 20 µg of misoprostol RS per mL.

Maintain the column temperature at 35°C.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 200 nm. Store the samples at 4°C during analysis, using a cooled autosampler.

Inject alternately 100 µL each of solutions (1) and (2). The test is not valid unless the symmetry factor of the peak due to misoprostol is between 0.8 and 1.5.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of misoprostol \(\text{C}_{22}\text{H}_{38}\text{O}_5\) in the dispersion, using the declared content of \(\text{C}_{22}\text{H}_{38}\text{O}_5\) in misoprostol RS.

**Impurities**

The impurities limited by the requirements of this monograph are those listed in the monograph for Misoprostol.

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\(^3\) An Ascentis Express C18 column was found suitable.
Misoprostol tablets
(Misoprostoli compressi)

This is a draft proposal for The International Pharmacopoeia (Working document QAS/15.643, November 2015).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidt@who.int.

[Note from the Secretariat. The following monograph is proposed for inclusion in The International Pharmacopoeia.]

**Category.** Prostaglandin (PGE₁), analogue.

**Storage.** Misoprostol tablets should be kept in tightly closed containers, protected from humidity.

**Additional information.** Strength in the current WHO Model list of essential medicines: 100 μg, 200 μg.

**Requirements**

Comply with the monograph for Tablets.

Misoprostol tablets contain not less than 90.0% and not more than 110.0% of the amount of C₂₂H₃₈O₅ stated on the label.

**Identity tests**

Either test A or B may be applied.

**A.** Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”. The retention time of the principal peak in the chromatogram obtained from solution (1) corresponds to the retention time of the peak due to misoprostol in the chromatogram obtained from solution (2).

**B.** Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R3 as the coating substance and a mixture of 8 volumes of toluene R, 2 volumes of ethyl acetate R, 1 volume of dehydrated ethanol R and 0.1 volume of glacial acetic acid R as the mobile phase, prepared immediately before use. Apply separately to the plate 100 μL of each of the following two solutions in dehydrated ethanol R. For solution (1) shake mechanically a quantity of the powdered tablets equivalent to 1 mg of misoprostol with 10 mL of dehydrated ethanol R for 10 minutes, filter and use the clear filtrate. For solution (2) use 0.1 mg of misoprostol RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air, expose it to the vapour of iodine R and examine the chromatogram in daylight.

The principal spot obtained with solution (1) corresponds in position, appearance and intensity to that obtained with solution (2).
Dissolution. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms using as the dissolution medium 500 mL of purified water and rotating the paddle at 50 revolutions per minute. At 30 minutes withdraw a sample of 10 mL of the medium through an in-line filter. Allow the filtered sample to cool to room temperature (solution (A)). For solution (B) dilute a suitable volume of solution (2) described under “Assay” with water R to obtain a concentration of 0.2 μg of misoprostol per mL for 100 μg tablets and 0.4 μg of misoprostol per mL for 200 μg tablets.

Carry out the test as described under 1.14.4 High-performance liquid chromatography using the method described under “Assay”. Inject 250 μL each of solutions (A) and (B) and measure the areas of the peak responses corresponding to misoprostol obtained in the chromatograms.

For each of the tablets tested calculate the total amount of misoprostol (C_{22}H_{38}O_{5}) in the medium from the peak areas obtained using the declared content of C_{22}H_{38}O_{5} in misoprostol RS. Use the requirements as described under 5.5 Dissolution test for solid oral dosage forms. Acceptance criteria to evaluate the results: the amount in solution is not less than 80% (Q) of the amount declared on the label.

Related substances

Prepare fresh solutions and perform the tests without delay.

Carry out the test as described under 1.14.4 High performance liquid chromatography using a stainless steel column (15 cm × 4.6 mm) packed with octadecylsilyl silica gel (5 μm).\(^1\)

Use the following conditions for gradient elution:

- Mobile phase A: mix 28 volumes of acetonitrile for chromatography R with 69 volumes of water R and 3 volumes of methanol R.
- Mobile phase B: mix 47 volumes of acetonitrile for chromatography R with 50 volumes of water R and 3 volumes of methanol R.

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–5</td>
<td>100</td>
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<td>isocratic</td>
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<td>linear gradient</td>
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<td>35 to 100</td>
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<td>100 to 0</td>
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</tr>
<tr>
<td>32–40</td>
<td>100</td>
<td>0</td>
<td>re-equilibration</td>
</tr>
</tbody>
</table>

Maintain the column temperature at 35°C.

Prepare the following solutions using a mixture of 31 volumes of acetonitrile R and 69 volumes of water as solvent. For solution (1) weigh and powder 20 tablets, mix a quantity of the powder equivalent to about 2000 μg of misoprostol, accurately weighed, with 10.0 mL of acetonitrile R and sonicate for about 10 minutes. Ensure that the temperature of the sonication bath is below room temperature to avoid degradation of misoprostol. Centrifuge and filter the supernatant. Evaporate 6.0 mL of the filtrate to dryness with nitrogen and dissolve the residue in 3.0 mL of solvent, using a vortex mixer. For solution (2) dilute 1 volume of solution (1) to 200 volumes. For solution (3) heat 1 mL of solution (1) in a water bath at 75°C for 1 hour.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 200 nm. Store the samples at 4°C during analysis, using a cooled autosampler.

\(^1\) An Ascentis Express C18 column was found suitable.
Inject 200 μL of solution (3). The test is not valid unless the peak-to-valley ratio (Hp/Hv) is at least 5.0, where Hp is the height above the extrapolated baseline of the peak due to impurity A (with a relative retention of about 0.95 with reference to misoprostol (retention time about 21 minutes) and Hv is the height above the extrapolated baseline at the lowest point of the curve separating the peak due to impurity A from the peak due to misoprostol.

Inject alternately 200 μL each of solutions (1) and (2).

The chromatogram obtained with solution (1) may show the following impurities at the following relative retentions with reference to misoprostol (retention time about 21 minutes): impurity E (1st peak): about 0.84; impurity E (2nd peak): about 0.86; impurity B (1st peak): about 0.90; impurity B (2nd peak): about 0.92; impurity A: about 0.95; impurity D: about 1.27; impurity C: about 1.37. Use also the chromatogram obtained with solution (3) to identify impurity A and C.

In the chromatogram obtained with solution (1):
• the sum of the areas of any peak corresponding to impurity A, B and E is not greater than 6 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%);
• the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.76, is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);
• the area of any peak corresponding to impurity D is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Assay

Carry out the test as described under 1.14.4 High performance liquid chromatography using a stainless steel column (15 cm × 4.6 mm) packed with octadecylsilyl silica gel (5 μm). As the mobile phase use a mixture of 45 volumes of acetonitrile R and 55 volumes of water R.

Prepare the following solutions in the mobile phase. For solution (1) weigh and powder 20 tablets, weigh accurately a quantity of the powder equivalent to about 400 μg of misoprostol in a 20.0 mL volumetric flask. Add about 10 mL and sonicate for 10 minutes. Ensure that the temperature of the sonication bath is below room temperature to avoid degradation of misoprostol and make up to volume. Filter a portion of this solution, discarding the first few mL of the filtrate. For solution (2) use 20 μg of misoprostol RS per mL.

Maintain the column temperature at 35°C.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 200 nm. Store the samples at 4°C during analysis using a cooled autosampler.

Inject alternately 100 μL each of solutions (1) and (2).

The test is not valid unless the symmetry factor of the peak due to misoprostol is between 0.8 and 1.5.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of misoprostol C_{22}H_{38}O_{5} in the tablets, using the declared content of C_{22}H_{38}O_{5} in misoprostol RS.

Impurities

The impurities limited by the requirements of this monograph are those listed in the monograph for Misoprostol.

***

2 An Ascentis Express C18 column was found suitable.
Carbamazepine
(Carbamazepinum)

This is a revised draft proposal for The International Pharmacopoeia (Working document QAS/15.608/Rev.1, December 2015).

The working document with line numbers and tracked changes is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

[Note from the Secretariat. It is proposed to revise the monograph on Carbamazepine in The International Pharmacopoeia. Comments are in particular sought as to whether the impurities listed under the section Impurities are degradation products or synthesis impurities.]

[Note from the editor. In accordance with WHO editorial policy the text reproduced below does not include tracked changes. Changes from the current monograph are indicated by insert and delete in the working document available at the above-mentioned web address.]

Molecular formula. \(C_{15}H_{12}N_2O\)

Relative molecular mass. 236.3

Graphic formula.

![Graphic formula of Carbamazepine](image)

Chemical name. 5H-Dibenz[b,f]azepine-5-carboxamide; CAS Reg. No. 298-46-4.

Description. A white to almost white, crystalline powder.

Solubility. Very slightly soluble in water; sparingly soluble in acetone; soluble in ethanol (~750 g/L) TS; freely soluble in dichloromethane.

Category. Antiepileptic.

Additional information. Carbamazepine exhibits polymorphism. The acceptable crystalline form is anhydrous polymorph form III\(^1\). It corresponds to carbamazepine RS.

Storage. Carbamazepine should be kept in a tightly closed container.

Requirements

Definition. Carbamazepine contains not less than 98.0% and not more than 102.0% of \(C_{15}H_{12}N_2O\), calculated with reference to the dried substance.

Identity tests

- Either test A or any two of tests B, C and D may be applied.
  
  A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum obtained from the test substance without pretreatment is concordant with the spectrum obtained from carbamazepine RS or with the reference spectrum of carbamazepine.

  B. Carry out test B.1 or, where UV detection is not available, test B.2.

  B.1. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 78 volumes of toluene R and 22 volumes of methanol R as the mobile phase. Apply separately to the plate 2 μL of each of the following three solutions, prepared using a mixture of equal volumes of ethanol (~750 g/L) TS and dichloromethane R. For solution (A) use 5 mg of the test substance per mL. For solution (B) use 5 mg of carbamazepine RS per mL. For solution (C) use 5 mg of carbamazepine RS and 5 mg of diazepam R per mL. After removing the plate from the chromatographic chamber allow it to dry in air and examine the chromatogram in ultraviolet light (254 nm).

  The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with solution (C) shows 2 clearly separated spots.

  B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography using the conditions described under test B.1 but using a plate containing silica gel R5 as the coating substance.

  After removing the plate from the chromatographic chamber allow it to dry in air. Spray the plate with potassium dichromate TS3, then heat it at 105°C for 15 minutes. Examine the chromatogram in daylight.

  The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with solution (C) shows 2 clearly separated spots.

  C. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”, Method B. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to carbamazepine in the chromatogram obtained with solution (2).

  D. Heat 0.1 g with 2 mL of nitric acid (~1000 g/L) TS in a water-bath for 3 minutes; an orange-red colour is produced.

Chlorides. For the preparation of the test solution boil 3.57 g in 50 mL of water for 10 minutes, cool, again adjust the volume, filter. To 25 mL of the filtrate add 10 mL of nitric acid (~130 g/L) TS and proceed as described under 2.2.1 Limit test for chlorides; the chloride content is not more than 0.14 mg/g.

Heavy metals. Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 3; determine the heavy metals content according to Method A; not more than 10 μg/g.

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry to constant weight at 105°C; it loses not more than 5.0 mg/g.
**Acidity or alkalinity.** To 1.0 g add 20 mL of carbon-dioxide-free water R, shake for 15 minutes and filter. To 10 mL of the filtrate add 0.05 mL of phenolphthalein/ethanol TS and 0.5 mL of carbonate-free sodium hydroxide (0.01 mol/L) VS; the solution is red. Add 1.0 mL of hydrochloric acid (0.01 mol/L) VS; the solution is colourless. Add 0.15 mL of methyl red/ethanol TS; the solution is red.

**Related substances.** Carry out the test as described under 1.14.4 High-performance liquid chromatography using the chromatographic conditions given under “Assay, method B”.

Prepare the following solutions. For solution (1) dissolve about 75 mg of the test substance in 25 mL of methanol R, sonicate and dilute to 50 mL with water R. For solution (2) dilute 1 volume of solution (1) to 1000 volumes with a mixture of equal volumes of methanol R and water R. For solution (3) use a solution containing 10 µg of carbamazepine RS and 10 µg of carbamazepine impurity A RS per mL of a mixture of equal volumes of methanol R and water R. For solution (4) use a solution containing 10 µg of iminodibenzyl R (impurity E) per mL.

Inject 20 µL of solution (3). The test is not valid unless the resolution between carbamazepine and carbamazepine impurity A is not less than 1.7.

Inject alternately 20 µL each of solutions (1), (2) and (4). Record the chromatograms for eight times the retention time of carbamazepine. In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to carbamazepine (retention time about 9 minutes): impurity A about 0.9; impurity D about 2.1; and impurity E about 3.5. Use the chromatogram obtained with solution (3) to identify the peak due to impurity A and the chromatogram obtained with solution (4) to identify the peak due to impurity E.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 2.8, is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);
- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 0.4, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 2.7, is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);
- the area of any other impurity peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.10%);
- the sum of the corrected areas of the peaks corresponding to impurity A, impurity D and impurity E and the areas of all other peaks, other than the principal peak, is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%). Disregard any peak with an area less than 0.5 times the area of the principal peak obtained with solution (2) (0.05%).

**Assay**

- Either method A or B may be applied.

  A. Dissolve about 0.1 g, accurately weighed, in sufficient ethanol (~750 g/L) TS to produce 100.0 mL. Dilute 10.0 mL of this solution to 100.0 mL with the same solvent, and again dilute 10.0 mL of this dilution to 100.0 mL with ethanol (~750 g/L) TS. Measure the
absorbance (1.6) of a 1 cm layer of the resulting solution at the maximum at about 285 nm. Calculate the percentage content of C_{15}H_{12}N_{2}O in the substance being tested, using the absorptivity value of 49.0 (A_{1cm}^{1%} = 490).

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded cyanopropyl groups (10 μm). As the mobile phase use a mixture of 30 volumes of tetrahydrofuran R, 120 volumes of methanol R, 850 volumes of water R, 0.2 volume of anhydrous formic acid R and 0.5 volume of triethylamine R.

Operate with a flow rate of 2.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 230 nm.

Prepare the following solutions. For solution (1) dissolve about 10 mg of the test substance, accurately weighed, in 25 mL of methanol R, sonicate and dilute to 50.0 mL with water R. For solution (2) use carbamazepine RS to obtain a solution containing 0.2 mg per mL of equal volumes of methanol R and water R.

Inject alternately 20 μL each of solution (1) and (2). The assay is not valid unless the column efficiency (N) is at least 5000, determined for the peak due to carbamazepine in the chromatogram obtained with solution (2).

Measure the areas of the peaks corresponding to carbamazepine obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of carbamazepine (C_{15}H_{12}N_{2}O) in the samples using the declared content of C_{15}H_{12}N_{2}O in carbamazepine RS.

**Impurities**

A. 10,11-dihydro-dibenzo[b,f]azepine-5H-carboxamide (10,11-dihydrocarbamazepine) (synthesis impurity)

B. 9-methylacridine

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2 A Nucleosil 100-10 CN column was found suitable.
C. (5H-dibenzo[b,f]azepin-5-ylcarbonyl)urea (N-carbamoylcarbamazepine)

D. 5H-dibenzo[b,f]azepine (iminostilbene)

E. 10,11-dihydro-5H-dibenzo[b,f]azepine (iminodibenzyl)

F. 5H-dibenzo[b,f]azepine-5-carbonyl chloride (5-chlorocarbonyliminostilbene)

G. 10-bromo-5H-dibenzo[b,f]azepine-5-carboxamide (10-bromocarbamazepine)

**Reagent to be established**
Diazepam R
Diazepam of a suitable quality should be used.
Carbamazepine tablets

(Carbamazepini compressi)

This is a revised draft proposal for The International Pharmacopoeia (Working document QAS/15.632/Rev.1, December 2015).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/.

Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidt@who.int.

[Note from the Secretariat. It is proposed to revise the monograph on Carbamazepine tablets in The International Pharmacopoeia.]

Category. Antiepileptic.

Storage. Carbamazepine tablets should be kept in a tightly closed container.

Additional information. Strength in the current WHO Model list of essential medicines (EML): 100 mg, 200 mg. Strength in the current WHO EML for children: 100 mg, 200 mg.

Requirements

Complies with the monograph for Tablets.

Definition. Carbamazepine tablets contain not less than 90.0% and not more than 110.0% of the amount of carbamazepine (C\textsubscript{15}H\textsubscript{12}N\textsubscript{2}O) stated on the label.

Identity tests

• Either test A alone or any two of tests B, C and D may be applied

Transfer a quantity of the powdered tablets equivalent to about 0.25 g of carbamazepine to a 50 mL beaker, add 15 mL of acetone R and boil the solution. Filter while hot, evaporate the filtrate to dryness on a water-bath and dry at 80°C for 30 minutes. Dissolve in acetone R, allow to recrystallize and use the crystals for the following tests.

A. Carry out the examination with the crystals as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from carbamazepine RS or with the reference spectrum of carbamazepine.

B. Carry out test B.1 or, where UV detection is not available, test B.2.

B.1. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 78 volumes of toluene R and 22 volumes of methanol R as the mobile phase. Apply separately to the plate 2 μL of each of the following three solutions, prepared using as a solvent a mixture of equal volumes of ethanol (~750 g/L) TS and dichloromethane R. For solution (A) use 5 mg of the crystals per mL. For solution (B) use 5 mg of carbamazepine RS per mL. For solution (C) use 5 mg of carbamazepine RS and 5 mg of diazepam R per mL. After removing the plate from the chromatographic chamber allow it to dry in air and examine the chromatogram in ultraviolet light (254 nm).
The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with solution (C) shows 2 clearly separated spots.

B.2 Carry out the test as described under Thin-layer chromatography using the conditions described under test B.1 but using a plate containing silica gel R5 as the coating substance.

After removing the plate from the chromatographic chamber allow it to dry in air. Spray the plate with potassium dichromate TS3 then heat the plate at 105°C for 15 minutes. Examine the chromatogram in daylight.

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with solution (C) shows 2 clearly separated spots.

C. Carry out the test as described under High-performance liquid chromatography, using the conditions given under “Assay”, Method B. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to carbamazepine in the chromatogram obtained with solution (2).

D. Heat 0.1 g of the crystals with 2 mL of nitric acid (~1000 g/L) TS in a water-bath for 3 minutes; an orange-red colour is produced.

Related substances. Carry out the test as described under High-performance liquid chromatography using the conditions given below under Assay B.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 0.15 g of carbamazepine into a 100 mL volumetric flask, shake with 50 mL of methanol R for about 15 minutes, dilute to volume with water R and filter. For solution (2) dilute 1 volume of solution (1) to 500 volumes with equal volumes of methanol R and water R. For solution (3) use a solution containing 10 µg of carbamazepine RS and 10 µg of carbamazepine impurity A RS per mL of a mixture of equal volumes of methanol R and water R.

Inject 20 µL of solution (3). The test is not valid unless the resolution between carbamazepine and carbamazepine impurity A is not less than 1.7.

Inject alternately 20 µL each of solution (1) and solution (2). Record the chromatograms for four times the retention time of carbamazepine. In the chromatogram obtained with solution (1) the following impurity, if present, is eluted at the following relative retention with reference to carbamazepine (retention time about 9 minutes): impurity D about 2.1.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 0.4, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Dissolution. Carry out the test as described under Dissolution test for solid oral dosage forms using as the dissolution medium 900 mL of a 1% solution of sodium dodecyl sulfate R in water and rotating the paddle at 75 revolutions per minute. At 60 minutes withdraw a sample of about 10 mL of the medium through an in-line filter. Allow the filtered sample to cool to room temperature. Measure the absorbance (1.6) of a 1 cm layer of the filtered sample, suitably diluted if necessary, at the maximum at about 288 nm.
For each of the tablets tested calculate the amount of carbamazepine \((\text{C}_{15}\text{H}_{12}\text{N}_2\text{O})\) in the medium using the absorptivity value of 49.0 \((\text{A}_{1\text{cm}} = 490)\). Evaluate the results as described under 5.5 Dissolution test for solid dosage forms, Acceptance criteria.

The amount of carbamazepine in solution for each tablet is not less than 75\% (Q) of the amount declared on the label.

**Assay**

- Either method A or B may be applied.

**A.** Weigh and powder 20 tablets. To an accurately weighed quantity of the powder, containing about 0.06 g of carbamazepine, add 25 mL of ethanol \((\sim 750 \text{ g/L})\) TS and boil for a few minutes. Stir the hot mixture in a closed flask for 10 minutes and filter. Wash the flask with ethanol \((\sim 750 \text{ g/L})\) TS, filter and dilute the cooled filtrate with sufficient ethanol \((\sim 750 \text{ g/L})\) TS to produce 100.0 mL. Dilute 5.0 mL to 250.0 mL with the same solvent.

  Measure the absorbance of a 1 cm layer of the solution at the maximum at about 285 nm against a solvent cell containing ethanol \((\sim 750 \text{ g/L})\) TS. Calculate the content of \(\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}\) using the absorptivity value of 49.0 \((\text{A}_{1\text{cm}} = 490)\).

**B.** Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column \((25 \text{ cm} \times 4.6 \text{ mm})\), packed with particles of silica gel, the surface of which has been modified with chemically-bonded cyanopropyl groups \((10 \mu\text{m})\).\(^1\) As the mobile phase use a mixture of 30 volumes of tetrahydrofuran R, 120 volumes of methanol R, 850 volumes of water R, 0.2 volume of anhydrous formic acid R and 0.5 volume of triethylamine R.

  Operate with a flow rate of 2.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 230 nm.

  Prepare the following solutions. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powder equivalent to about 0.1 g of carbamazepine to a 100 mL volumetric flask, add 50 mL of methanol R and sonicate for about 15 minutes. Allow to cool to room temperature, make up to volume with water R and filter the solution. Dilute 10.0 mL of the filtrate to 50.0 mL with a mixture of equal volumes of methanol R and water R. For solution (2) use carbamazepine RS to obtain a solution containing 0.2 mg per mL of equal volumes of methanol R and water R.

  Inject alternately 20 \(\mu\text{L}\) each of solution (1) and (2). The assay is not valid unless the column efficiency is at least 5000, determined for the peak due to carbamazepine in the chromatogram obtained with solution (2).

  Measure the areas of the peaks corresponding to carbamazepine and calculate the content of carbamazepine \((\text{C}_{15}\text{H}_{12}\text{N}_2\text{O})\) in the tablets using the declared content of \(\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}\) in carbamazepine RS.

**Impurities.** The impurity limited by the requirements of this monograph is impurity D listed in the monograph for carbamazepine.

**Reagent to be established**

Diazepam R

Diazepam of a suitable quality should be used.

\(^1\) A Nucleosil 100-10 CN column was found suitable.
Carbamazepine chewable tablets
(Carbamazepini compressi manducabili)

This is a revised draft proposal for The International Pharmacopoeia (Working document QAS/15.609/ Rev.1, December 2015).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/.

Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

[Note from the Secretariat. The following draft monograph on Carbamazepine chewable tablets is proposed for inclusion in The International Pharmacopoeia.]

Category. Antiepileptic.

Storage. Carbamazepine chewable tablets should be kept in a tightly closed container.

Additional information. Strengths in the current WHO Model list of essential medicines (EML): 100 mg, 200 mg. Strengths in the current WHO EML for children: 100 mg, 200 mg.

Requirements

Complies with the monograph for Tablets.

Definition. Carbamazepine chewable tablets contain Carbamazepine in a suitable basis that may contain suitable flavouring agents. Carbamazepine chewable tablets contain not less than 90.0% and not more than 110.0% of the amount of carbamazepine (C₁₅H₁₂N₂O) stated on the label.

Identity tests

• Either test A alone or any two of tests B, C and D may be applied

Transfer a quantity of the powdered tablets equivalent to about 0.25 g of carbamazepine to a 50 mL beaker, add 15 mL of acetone R and boil the solution. Filter while hot, evaporate the filtrate to dryness on a water-bath and dry at 80°C for 30 minutes. Dissolve in acetone R, allow to recrystallize and use the crystals for the following tests.

A. Carry out the examination with the crystals as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from carbamazepine RS or with the reference spectrum of carbamazepine.

B. Carry out test B.1 or, where UV detection is not available, test B.2.

B.1. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 78 volumes of toluene R and 22 volumes of methanol R as the mobile phase. Apply separately to the plate 2 μL of each of the following three solutions, prepared using as a solvent a mixture of equal volumes of ethanol (~750 g/L) TS and dichloromethane R. For solution (A) use 5 mg of the crystals per mL. For solution (B) use 5 mg of carbamazepine RS per mL. For solution (C) use 5 mg of carbamazepine RS and 5 mg of diazepam R per mL. After removing the plate from the chromatographic chamber allow it to dry in air and examine the chromatogram in ultraviolet light (254 nm).
The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with solution (C) shows 2 clearly separated spots.

B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography using the conditions described under test B.1 but using a plate containing silica gel R5 as the coating substance.

After removing the plate from the chromatographic chamber allow it to dry in air. Spray the plate with potassium dichromate TS3 then heat the plate at 105°C for 15 minutes. Examine the chromatogram in daylight.

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with solution (C) shows 2 clearly separated spots.

C. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under “Assay”, Method B. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to carbamazepine in the chromatogram obtained with solution (2).

D. Heat 0.1 g of the crystals with 2 mL of nitric acid (~1000 g/L) TS in a water-bath for 3 minutes; an orange-red colour is produced.

Related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given below under Assay B.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 0.15 g of carbamazepine into a 100 mL volumetric flask, shake with 50 mL of methanol R for about 15 minutes, dilute to volume with water R and filter. For solution (2) dilute 1 volume of solution (1) to 500 volumes with equal volumes of methanol R and water R. For solution (3) use a solution containing 10 µg of carbamazepine RS and 10 µg of carbamazepine impurity A RS per mL of a mixture of equal volumes of methanol R and water R.

Inject 20 µL of solution (3). The test is not valid unless the resolution between carbamazepine and carbamazepine impurity A is not less than 1.7.

Inject alternately 20 µL each of solution (1) and solution (2). Record the chromatograms for four times the retention time of carbamazepine. In the chromatogram obtained with solution (1) the following impurity, if present, is eluted at the following relative retention with reference to carbamazepine (retention time about 9 minutes): impurity D about 2.1.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 0.4, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Dissolution. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms using as the dissolution medium 900 mL of a 1% solution of sodium dodecyl sulfate R in water and rotating the paddle at 75 revolutions per minute. At 60 minutes withdraw a sample of about 10 mL of the medium through an in-line filter. Allow the filtered sample to cool to room temperature. Measure the absorbance (1.6) of a 1 cm layer of the filtered sample, suitably diluted if necessary, at the maximum at about 288 nm.
For each of the tablets tested calculate the amount of carbamazepine (C\textsubscript{15}H\textsubscript{12}N\textsubscript{2}O) in the medium using the absorptivity value of 49.0 (\(A_{1\text{cm}}^{1\%} = 490\)). Evaluate the results as described under 5.5 Dissolution test for solid dosage forms, Acceptance criteria.

The amount of carbamazepine in solution for each tablet is not less than 75\% (Q) of the amount declared on the label.

**Assay**

- Either method A or B may be applied.

A. Weigh and powder 20 tablets. To an accurately weighed quantity of the powder, containing about 0.06 g of carbamazepine, add 25 mL of ethanol (~750 g/L) TS and boil for a few minutes. Stir the hot mixture in a closed flask for 10 minutes and filter. Wash the flask with ethanol (~750 g/L) TS, filter and dilute the cooled filtrate with sufficient ethanol (~750 g/L) TS to produce 100.0 mL. Dilute 5.0 mL to 250.0 mL with the same solvent.

Measure the absorbance of a 1 cm layer of the solution at the maximum at about 285 nm against a solvent cell containing ethanol (~750 g/L) TS. Calculate the content of C\textsubscript{15}H\textsubscript{12}N\textsubscript{2}O using the absorptivity value of 49.0 (\(A_{1\text{cm}}^{1\%} = 490\)).

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm x 4.6 mm), packed with particles of silica gel, the surface of which has been modified with chemically-bonded cyanopropyl groups (10 \(\mu\)m).\(^1\) As the mobile phase use a mixture of 30 volumes of tetrahydrofuran R, 120 volumes of methanol R, 850 volumes of water R, 0.2 volume of anhydrous formic acid R and 0.5 volume of triethylamine R.

Operate with a flow rate of 2.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 230 nm.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powder equivalent to about 0.1 g of carbamazepine to a 100 mL volumetric flask, add 50 mL of methanol R and sonicate for about 15 minutes. Allow to cool to room temperature, make up to volume with water R and filter the solution. Dilute 10.0 mL of the filtrate to 50.0 mL with a mixture of equal volumes of methanol R and water R. For solution (2) use carbamazepine RS to obtain a solution containing 0.2 mg per mL of equal volumes of methanol R and water R.

Inject alternately 20 \(\mu\)L each of solution (1) and (2). The assay is not valid unless the column efficiency is at least 5000, determined for the peak due to carbamazepine in the chromatogram obtained with solution (2).

Measure the areas of the peaks corresponding to carbamazepine and calculate the content of carbamazepine (C\textsubscript{15}H\textsubscript{12}N\textsubscript{2}O) in the tablets using the declared content of C\textsubscript{15}H\textsubscript{12}N\textsubscript{2}O in carbamazepine RS.

**Impurities.** The impurity limited by the requirements of this monograph is impurity D listed in the monograph for carbamazepine.

**Reagent to be established**

Diazepam R
Diazepam of a suitable quality should be used.

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\(^1\) A Nucleosil 100-10 CN column was found suitable.
Carbamazepine oral suspension
(Carbamazepini suspensio peroralis)

This is a revised draft proposal for The International Pharmacopoeia (Working

The working document with line numbers is available for comment at
Please address any comments to: World Health Organization, Quality Assurance
and Safety: Medicines, Dr Herbert Schmidt, CH-1211 Geneva 27, Switzerland;
fax: +41 22 791 4730; email: schmidt@who.int.

[Note from the Secretariat. The following draft monograph on Carbamazepine oral solution is proposed
for inclusion in The International Pharmacopoeia.]

Category. Antiepileptic.

Storage. Carbamazepine oral suspension should be kept in tightly closed, light-resistant
containers, protected from freezing and from excessive heat.

Additional information. Strength in the current WHO Model list of essential medicines (EML):
100 mg per 5 mL. Strength in the current WHO EML for children: 100 mg per 5 mL.

Requirements
Complies with the monograph for Liquid preparations for oral use.

Definition. Carbamazepine oral suspension is a suspension of Carbamazepine in a suitable
vehicle, which may be flavoured. It contains not less than 90.0% and not more than 110.0% of
the amount of carbamazepine (C₁₅H₁₂N₂O) stated on the label.

Identity tests
• Either test A alone or any two of tests B, C and D may be applied.

Transfer a quantity of the oral suspension equivalent to about 0.25 g of carbamazepine to a
centrifuge tube, centrifuge and wash the precipitate with two quantities of 10 mL of water R.
Dissolve the precipitate as completely as possible in 10 mL of dichloromethane R, filter and
evaporate the filtrate to dryness in air, dry the residue at 80°C for 30 minutes and use it for the
following tests.

A. Carry out the examination with the residue as described under 1.7 Spectrophotometry
in the infrared region. The infrared absorption spectrum is concordant with the spectrum
obtained from carbamazepine RS or with the reference spectrum of carbamazepine.

B. Carry out test B.1 or, where UV detection is not available, test B.2.

B.1. Carry out the test as described under 1.14.1 Thin-layer chromatography using
silica gel R6 as the coating substance and a mixture of 78 volumes of toluene
R and 22 volumes of methanol R as the mobile phase. Apply separately to the
plate 2 μL of each of the following three solutions, prepared using as a solvent
in a mixture of equal volumes of ethanol (~750 g/L) TS and dichloromethane R.
For solution (A) use 5 mg of the residue per mL. For solution (B) use 5 mg of
 carbamazepine RS per mL. For solution (C) use 5 mg of carbamazepine RS and
5 mg of diazepam R per mL. After removing the plate from the chromatographic chamber allow it to dry in air and examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with solution (C) shows 2 clearly separated spots.

B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography using the conditions described under test B.1 but using a plate containing silica gel R5 as the coating substance.

After removing the plate from the chromatographic chamber allow it to dry in air. Spray the plate with potassium dichromate TS3 then heat the plate at 105°C for 15 minutes. Examine the chromatogram in daylight.

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with solution (C) shows 2 clearly separated spots.

C. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under “Assay”, Method B. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to carbamazepine in the chromatogram obtained with solution (2).

D. Heat 0.1 g of the residue with 2 mL of nitric acid (~1000 g/L) TS in a water-bath for 3 minutes; an orange-red colour is produced.

**pH value** (1.13). pH of the oral suspension, 3.5–4.5.

**Related substances.** Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given below under Assay B.

Prepare the following solutions. For solution (1), if necessary, shake the container of oral suspension to resuspend any settled material. Transfer a quantity of it, containing about 0.2 g of Carbamazepine, into a 100 mL volumetric flask, add 50 mL of methanol R and sonicate for about 15 minutes. Allow the suspension to cool to room temperature and dilute to volume with water R. Centrifuge 10 mL of the suspension. Transfer 5.0 mL of the supernatant to a 10 mL volumetric flask and dilute to volume with equal volumes of methanol R and water R. For solution (2) dilute 1 volume of solution (1) to 500 volumes with equal volumes of methanol R and water R. For solution (3) use a solution containing 10 µg of carbamazepine RS and 10 µg of carbamazepine impurity A RS per mL of a mixture of equal volumes of methanol R and water R.

Inject 20 µL of solution (3). The test is not valid unless the resolution between carbamazepine and carbamazepine impurity A is not less than 1.7.

Inject alternately 20 µL each of solution (1) and solution (2). Record the chromatograms for four times the retention time of carbamazepine. In the chromatogram obtained with solution (1) the following impurity, if present, is eluted at the following relative retention with reference to carbamazepine (retention time about 9 minutes): impurity D about 2.1.

In the chromatogram obtained with solution (1):
- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 0.4, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).
Assay

• Either method A or B may be applied.

A. If necessary, shake the container of oral suspension to resuspend any settled material. Transfer an accurately weighed quantity of it, containing about 0.1 g of Carbamazepine, to a 100 mL volumetric flask, add about 50 mL of ethanol (~750 g/L) TS and sonicate for about 15 minutes. Allow the suspension to cool to room temperature, dilute with the same solvent to volume and filter the solution. Dilute 1.0 mL of the filtrate to 100.0 mL with ethanol (~750 g/L) TS.

Measure the absorbance of a 1 cm layer of the solution at the maximum at about 285 nm against a solvent cell containing ethanol (~750 g/L) TS. Determine the weight per mL (1.3.1) of the oral suspension and calculate the content of C_{15}H_{12}N_{2}O, weight in volume, of the oral suspension using the absorptivity value of 49.0 (A_{1cm} = 490).

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm), packed with particles of silica gel, the surface of which has been modified with chemically-bonded cyanopropyl groups (10 μm). As the mobile phase use a mixture of 30 volumes of tetrahydrofuran R, 120 volumes of methanol R, 850 volumes of water R, 0.2 volume of anhydrous formic acid R and 0.5 volume of triethylamine R.

Operate with a flow rate of 2.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 230 nm.

Prepare the following solutions. For solution (1), if necessary, shake the container of oral suspension to resuspend any settled material. Transfer an accurately weighed quantity of it, containing about 200 mg of Carbamazepine, to a 100 mL volumetric flask, add 50 mL of methanol R and sonicate for about 15 minutes. Allow the suspension to cool to room temperature, dilute to volume with water R and filter the solution. Dilute 5.0 mL of the filtrate to 50.0 mL with equal volumes of methanol R and water R. For solution (2) use carbamazepine RS to obtain a solution containing 0.2 mg per mL of equal volumes of methanol R and water R.

Inject alternately 20 μL each solution (1) and (2). The assay is not valid unless the column efficiency is at least 5000, determined for the peak due to carbamazepine in the chromatogram obtained with solution (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2). Determine the weight per mL (1.3.1) of the oral suspension and calculate the content of carbamazepine (C_{15}H_{12}N_{2}O), weight in volume, of the oral suspension using the declared content of C_{15}H_{12}N_{2}O in carbamazepine RS.

Impurities. The impurity limited by the requirements of this monograph is impurity D listed in the monograph for carbamazepine.

Reagent to be established
Diazepam R
Diazepam of a suitable quality should be used.

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1 A Nucleosil 100-10 CN column was found suitable.