World Health Organization

A RISK-BASED IDENTIFICATION OF ESSENTIAL MEDICINES FOR LOCAL MANUFACTURING IN LOW-AND MIDDLE-INCOME COUNTRIES

(August 2016)

DRAFT FOR COMMENT

Should you have any comments on the attached text, please send these to: Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies, Standards and Norms, World Health Organization, 1211 Geneva 27, Switzerland; email: kopps@who.int, fax: (+41 22) 791 4730; and to Marie Gaspard (gaspardm@who.int), by **30 September 2016**.

Working documents are sent out electronically and they will also be placed on the Medicines website for comment. If you do not already receive directly our draft guidelines please let us have your email address (to bonnyw@who.int) and we will add it to our electronic mailing list.

SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/16.682:

A RISK-BASED IDENTIFICATION OF ESSENTIAL MEDICINES FOR LOCAL MANUFACTURING IN LOW-AND MIDDLE-INCOME COUNTRIES

Context: This document was developed as part of local production activities, supported by the European Commission and led by Dr Zafar Mirza, former Coordinator of the WHO Public Health, Innovation and Intellectual Property (PHI)	
Drafting of a practical guide entitled *Identification of non-biological essential medicines which has a potential for manufacturing in low and middle income countries with no to little manufacturing exposure (start-up situations) - Selection strategy based on a risk approach* by Professor T. Dekker	2015
Based on the above, a concept paper entitled *A framework for risk-based identification of essential medicine products for local manufacturing in low- and middle-income countries* was drafted by Ms D. Decina, WHO Regulatory Systems Strengthening (RSS). Developed as part of WHO's initiative, the activities of the local production team, in collaboration with UNIDO, to promote quality local production of medicines in developing countries. Publication in *WHO Drug Information* for comments	April 2016
Discussion of the concept paper and feedback received thereto during an informal consultation held with regulatory experts from national regulatory authorities and colleagues from UNIDO, PHI, the Prequalification Team(PQT), RSS and the Technologies Standards and Norms (TSN) teams	8–9 July 2016
Finalization of the working document QAS/16.682 for circulation based on feedback received by Ms D. Decina (RSS) and Dr S. Kopp (TSN), in collaboration with Professor T. Dekker	August 2016
Circulation of the working document for comments	August 2016
Presentation to fifty-first meeting of the WHO Expert	October 2016

Committee on Specifications for Pharmaceutical Preparations	
Any follow-up action, as needed	

[Note from the Secretariat:

Feedback is being sought as to whether this text could form part of the series of "Notes to consider" documents for pre-development within the context of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (for examples please see: http://www.who.int/medicines/areas/quality_safety/quality_assurance/development/en/), or whether it should rather be part of a wider framework for local manufacturing in low- and middle-income countries.

The text will be edited in accordance with WHO style if published within the WHO Technical Report Series.]

Introduction

A number of papers deal with a variety of aspects of the manufacture of medicines in low- and middle-income countries (LMICs) – including disease to be treated, capacity building, access to medicines, cost, skills, training, etc.; however, the technical level of what is to be produced in conjunction with the risk associated with the product itself is often not adequately addressed. Therefore a paper was prepared to fill this gap. The paper, which includes practical examples, is entitled *Identification of non-biological essential medicines which has a potential for manufacturing in low and middle income countries with no to little manufacturing exposure (start-up situations) - Selection strategy based on a risk approach.*

Based on the above a concept paper entitled *A framework for risk-based identification of essential medicine products for local manufacturing in low- and middle-income countries* was drafted. This concept paper aimed 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. The concept paper was based on the points addressed in the above practical guide, in a more general manner. It was published in *WHO Drug Information* for comments (http://www.who.int/medicines/publications/druginformation/WHO_DI_30-1_ConceptPaper.pdf?ua=1). This concept paper was developed as part of WHO's initiative, in collaboration with UNIDO, to promote quality local production of medicines in developing countries. The paper was proposed to be possibly combined in the future with another concept paper on a good manufacturing practices (GMP) roadmap – developed by UNIDO – into a document which could provide 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. UNIDO's GMP road mapping was also published in *WHO Drug Information* for comments.

Comments and suggestions on the first concept paper, the risk-based identification of essential medicine products for local manufacturing in low- and middle-income countries, were received and discussed at an informal consultation held by the Technologies Standards and Norms Team together with regulatory experts from national regulatory authorities, the Prequalification Team and the Regulatory Systems Strengthening Team in Copenhagen on 8-9 July 2016.

This working document is the outcome of the feedback received and the discussions held.

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 regulatory authority (NRA) to effectively assess the resultant dossier, to conduct inspections and to regulate life cycle variations. These activities by manufacturer and NRA 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)*[1].

The information and approaches provided in this document need to be considered along with the level of GMP (23) compliance at the site with respect to manufacture; the level of implementation and compliance to any related GXP (33), the acceptability of the quality standard applied to individual components (APIs) and the final dosage form; as well as the standards requested to be complied with by the NRA.

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 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].

[1] ANDA: Abbreviated New Drug Application (U.S. FDA)

[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)

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. Any radioactive preparations are also out of scope.

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 managed 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 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?

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

Table 1. **Risk ranking of product categories by potential loss of control**

Product category	Potential loss of state of control
Biotech	5
Liquids, sterile suspension/emulsion	5
Liquids, sterile solution	5
Metered dose inhalers, low and high API load*	5
Powders, low API load	4
Semisolids (ointment/cream), low API load	4
Solid orals, modified release, low API load	4
Transdermal	4
Liquids, non-sterile suspension/emulsion	3
Semisolids (ointment/cream), high API load	3
Solid orals, modified release, high API load	3
Solid orals, immediate release, low API load	3
Powders, high API load	2
Solid orals, immediate release, high API load	2
Liquids, non-sterile solution	1

* 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.

The Tran publication also discussed the categories listed in Table 1 with respect to contamination risk. For distinguishing risk factors within the product categories, see the publication.

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 2. **Classification of APIs according to the BCS**

Class	Solubility	Permeability
1	High	High
2	Low	High
3	High	Low
4	Low	Low

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

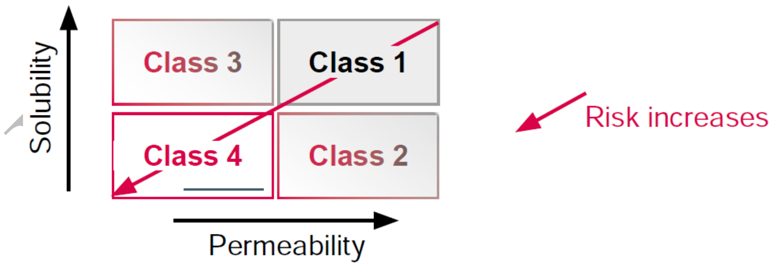
> *"An API is considered highly soluble when the highest single therapeutic dose as determined by the relevant regulatory authority, typically defined by the labelling for the innovator product, is soluble in 250 mL or less of aqueous media over the pH range of 1.2–6.8. The pH-solubility profile of the 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 web site[3].

---

[3] http://apps.who.int/prequal/info_applicants/BE/2014/BW_general_2014November.pdf

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 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 of, 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. 5 mg or less), desired smoothness in ophthalmic preparations and stability of suspensions *(20)*. 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. FPPs containing APIs with known critical polymorphism issues, such as ritonavir, should be categorized as a high risk. Such APIs may require special manufacturing techniques and control of the polymorphic form throughout the FPP manufacturing process.

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 used as test product in the BE study. 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)*.

Hygroscopicity and moisture sensitivity

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. APIs may also exhibit undesirable changes when exposed to a moist environment, including hydrolysis or reaction with other components of the dosage form formulation. Manufacture of a product containing a highly hygroscopic to deliquescent or moisture sensitive 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. Hygroscopicity should be determined using a standard test such as is described in PhEur and BP. Using such a test allows for a reliable, standard measure of hygroscopicity.

Stability

Stability is regarded as a relative term. API stability considerations are provided as a guide for risk assessment. API stability is dependent on the method of manufacture as well as the storage conditions and container system in which stability was determined. Therefore judging API stability based on literature data may not be reliable. 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, but must be considered in conjunction with all important factors, including the conditions, packaging and region where the stability was established.

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.

Manufacturing development and quality risks are most effectively mitigated through product knowledge. Candidate products with APIs for which individual monographs exist in major pharmacopoeias, can therefore be more favourable candidates since these individual API monographs may provide information on expected impurities, or desired physiochemical properties.

The quality of APIs can be further assured by selecting an API that is prequalified by the WHO, or has a current a Certificate of suitability of Monographs of the European Pharmacopoeia (CEP). Prequalified APIs have been demonstrated to meet WHO quality standards and to be manufactured in accordance with WHO GMP standards. A valid CEP identifies that the quality of the API can be adequately controlled, if the tests and analytical methods specified in the relevant individual API monograph of the European Pharmacopoeia, together with any tests specified in the CEP itself, are applied.

The WHO Prequalification Team – Medicines (WHO-PQTm) website[5] 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. A list of valid CEPs may be found on the European Directorate for the Quality of Medicines & HealthCare (EDQM) website[4].

Availability and continuity of supply of the API are also important considerations. Selected API manufacturers must be able to support any subsequent national market authorization submission and have a proven record of supply. 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).

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, such as 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 (see *Table 1)*, and have the highest contamination risk. 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. Consideration should be given to the risk analysis concepts in ICH Q3D for elemental impurities (EIs), for example the EIs of highest toxicity class (class 1) are typically present in mined excipients; common examples include talc and titanium dioxide. Minimizing mined excipients in the formulation would therefore minimize the potential for these EIs from excipient sources.

Risks to consider for final dosage form

Finished pharmaceutical products

Dosage form manufacturing process 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, dispersing, 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 or suspension, 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, complex technologies such as hot melt extrusion 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. 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 all the following are met: the APIs are of Class 1 or 3, a monograph in *The International Pharmacopoeia*, British Pharmacopoeia, United States Pharmacopeia or other official NMRA pharmacopoeia is available for the particular FDC and 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.

For products where a score line is required due to posology considerations, manufacturing skill is required to produce a product that can be uniformly split into the required portions.

Formulation

The complexity of the formulation of the finished pharmaceutical product (FPP) al product usually aligns with the technological capability requirements for FPP 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 formulation and 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. The storage instructions and assigned shelf life of the comparator or other multisource products may provide some indication of the stability of the FPP. However, note that even when a product is reverse-engineered from another product and is to be stored in similar packaging, the stability of the two products may be very different. Only a formal stability study can establish the stability of an individual product.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 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.

Additional considerations for manufacturing

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 **FPP** 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, dissolving and filling for liquid non-sterile solutions. As complexity increases through operations such as emulsion, granulation, dispersing, 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, granulation endpoints, 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. However, strictly meeting specifications and methods where pharmacopoeial monographs for the API or the finished products exist may not ensure sufficient comparability and quality for a biological product.

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. Other environmental factors than moisture can also have an impact on manufacturability and stability, including light sensitivity and oxygen sensitivity, and should be considered in the risk analysis. 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 to product cross-contamination, the safety of personnel needs to be considered adequately (33, http://www.who.int/occupational_health/healthy_workplaces/en/). 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 for APIs and FPPs

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 FPPs 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 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.,

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. The potential API manufacturer(s) should be qualified in this respect and the open part of APIMF/DMF well evaluated. 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.

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 its 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 candidate products 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 level of training and number of technical staff 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 NRA 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 NRA 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 NRA. 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 NRA of the country in which it is produced. Therefore, the capacity of the NRA should be included as a component of the local manufacturing feasibility assessment, and wherever possible an open dialogue between the potential manufacturer and the NRA 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. Additional requirements, such as quality systems maintenance and their sustainability, will need to be considered, to be able to confirm a state of control. 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

During the risk assessment using the templates below all sources of information which have contributed to the evaluation should be documented and referenced.

Primary information on candidate product

Candidate product (INN, dosage form, strength)	
Listed in EML/EMLc?	
BCS classification of API (provide supportive reference)	
Relative manufacture risk ranking (*Table 1*)	
Where risk ranking (according to Table 1) 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.

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

Question	**Answer**	**Additional comments**
Comparator product available?		
Comparator product name (brand/dosage form/strength) Indicate all available strengths		
Country/region of comparator product information		
Qualitative composition, if available (only core for immediate release coated tablets)		
List excipients that may affect bioavailability (BA)		
Quantities provided of excipients that may affect BA? (Yes/No. If Yes, provide quantities)		
If tablets, are they coated? What is the function of the coating?		
Primary packaging		
Storage conditions		
Shelf life, if available		
Other comments on comparator of importance for selection process, if any		
May a biowaiver be possible for candidate product? (If yes, clarify briefly)		

775

776

777 **Risk assessment for candidate product**

778 Scores from 1 (low risk) to 4 (high risk) and 5 (not recommended)

Item No.	Aspects to consider	Dosage form affected	Risk assessment guide	Score 1 to 5
Active pharmaceutical ingredient				
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 = 3 (The correct certification procedures should be followed). Otherwise score = 1	
A3	Monograph/specifications	All	If the API has a pharmacopoeial monograph (33), score = 1	

Item No.	Aspects to consider	Dosage form affected	Risk assessment guide	Score 1 to 5
			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	Polymorphism	Solid dosage forms	If the API has known critical polymorphism issues, score = 5 Otherwise score = 1	
A5	Hygroscopicity and moisture sensitivity	Solid dosage forms	Highly hygroscopic to deliquescent or moisture sensitivity, 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 a shelf life (not retest period) is allocated, score = 3 Otherwise score = 0	

Item No.	Aspects to consider	Dosage form affected	Risk assessment guide	Score 1 to 5
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 supplier is well-established and the API is readily available with no history of supply issues, score = 2 If the API is prequalified and/or has a CEP, score = 1 If the API supplier is not well-established and there is no prior agreement on sourcing, score = 5	
Excipients, including those that are removed during manufacture				
E1	Monograph/specifications	All	If the excipients have pharmacopoeial monographs, score = 1 Otherwise, score = 5	
E2	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	
Finished pharmaceutical product				

Item No.	Aspects to consider	Dosage form affected	Risk assessment guide	Score 1 to 5
F1	Dosage form	All	From *Table 1*: If the risk ranking for loss of control is 1 or 2, score = 1 If the risk ranking for loss of control is 3, score = 3 If the dosage form is complex and risk ranking for loss of control ≥ 4, score = 5 If the product is a fixed-dose combination and the APIs are all Class 1 or 3, score = 3 If the product is a fixed-dose combination and one or more APIs are not Class 1 or 3, score = 5 If the product is a fixed-dose combination and the actives are considered incompatible, score = 5	
F2	Composition	All	If the quantitative composition of the comparator is known, score = 1 If the qualitative composition of the comparator is known, score = 2 Otherwise score = 5	
F3	Monograph/specifications	All	If a pharmacopoeial monograph for the product is available,	

Item No.	Aspects to consider	Dosage form affected	Risk assessment guide	Score 1 to 5
			score = 1 If pharmacopoeial specifications require a surfactant in the dissolution medium, score = 5 Otherwise score = 5	
F4	Primary packaging	All	If the primary packaging is critical to accurate dosing score = 5 (e.g. metered dose inhalers) If the product is sterile, score = 5 If the manufacturer cannot do the packaging as required by comparator or other generic products, score = 3, otherwise score = 1.	
F5	Stability, storage and transport	All	The storage instructions of the comparator or other multisource products, e.g. WHO-prequalified products, can be used as indication of stability. If the product requires protective packaging, score = 3 (The final product must be stable enough to be stored under the conditions required by the NRA, Zone II, III, IVa or	

Item No.	Aspects to consider	Dosage form affected	Risk assessment guide	Score 1 to 5
			IVb). If storage instruction is "store in refrigerator" or lower temperature, score = 4, otherwise score = 1.	
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, and the intended formulation is qualitatively and quantitatively the same with regard to the agents score = 1 Otherwise score = 1	

779

780

Outcome of the risk assessment exercise

Candidate product (INN, dosage form, strength):		
	Answer	**Comments**
Any aspect scoring 5 (not recommended)		
Any **one** or more aspects scoring 4 (high risk)		
Any **two** or more aspects scoring 3(high risk)		
One scoring 3, rest 2 or below (medium risk)		
All scoring 2 or below (low risk)		
Candidate for further development, based on a low risk assessment (Yes/No)		

References

1 Attridge CJ, Preker AS. Improving access to medicines in developing countries - Application of new institutional economics to the analysis of manufacturing and distribution issues. Health, Nutrition and Population Discussion (HNP) Discussion Paper. Washington, USA: The World Bank; 2005.

2 Kaplan WA, Laing R. Local production of pharmaceuticals: Industrial policy and access to medicines – An overview of key concepts, issues and opportunities for future research. HNP Discussion Paper. Washington: The World Bank; 2005.

3 Kaplan WA. Local production and access to medicines in low- and middle-income countries - A literature review and critical analysis. Geneva: World Health Organization; 2011.

4 Moon S. Pharmaceutical production and related technology transfer. Geneva: World Health Organization; 2011.

5 Abbott FM. Trends in local production of medicines and related technology transfer. Geneva: World Health Organization; 2011.

6 African Union. Pharmaceutical manufacturing plan for Africa. Third session of the African Union Conference of Ministers of Health, Johannesburg, South Africa, 9–13 April 2007.

7 WHO. The Selection and Use of Essential Medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children). WHO Technical Report Series No 994. Geneva, World Health Organization; 2015.

8 WHO. Pharmaceutical development of multisource (generic) pharmaceutical products - points to consider. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-sixth report. Geneva, World Health Organization; 2012: Annex 3 (WHO Technical Report Series, No. 970);.

9 WHO. Development of paediatric medicines: points to consider in formulation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-sixth report. Geneva, World Health Organization; 2012: Annex 5 (WHO Technical Report Series, No. 970).

10 ICH. Q8(R2): Pharmaceutical development. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2009.

11 US-FDA. Quality by design for ANDAs: An example for immediate-release dosage forms. 2012

12 WHO. WHO guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh report. Geneva, World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981).

13 ICH. Q9: Quality risk management. International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2005.

14 Tran NL, Hasselbalch B., Morgan K. Claycamp G. Elicitation of expert knowledge about risks associated with pharmaceutical manufacturing processes. Pharmaceutical Engineering. 2005;25-10.

15 US-FDA. Guidance for industry – Immediate Release Solid Oral Dosage Forms. Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation. 1995.

16 US-FDA. Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. 2000. [Under revision]

17 WHO. Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report. Geneva, World Health Organization; 2006: Annex 8 (WHO Technical Report Series, No. 937). [Under revision]

18 WHO. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth report. Geneva, World Health Organization; 2015: Annex 7 (WHO Technical Report Series, No. 992).

19 EMA. Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). Committee for Medicinal Products for Human Use (CHMP). European Medicines Agency; 2010.

20 WHO. Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth report. Geneva, World Health Organization; 2014: Annex 6 (WHO Technical Report Series, No. 986).

21 WHO. Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report. Geneva, World Health Organization; 2009: Annex 4 (WHO Technical Report Series, No. 953).

22 WHO. WHO GMP for Biological Products. 2015. Proposed replacement of: TRS 822, Annex 1 as adopted by the Sixty-sixth Meeting of the World Health Organization Expert Committee on Biological Standardization, 12- 16 October 2015.

23 WHO. WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth report. Geneva, World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986).

24 EC. Risk assessment methodologies and approaches for genotoxic and carcinogenic substances. European Commission, Health & Consumer Protection Directorate-General; 2009.

25 US-FDA. Guidance for industry – Genotoxic and carcinogenic impurities in drug substances and products: Recommended approaches (draft guidance). 2008.

26 EMA. Questions and answers on the 'Guideline on the limits of genotoxic impurities' (EMA/CHMP/SWP/431994/2007 Rev. 3). Committee for Medicinal Products for Human Use (CHMP). European Medicines Agency; 2010.

27 ICH. S2(R1): Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use. International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2011.

28 ICH. M7: Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk (Draft consensus guideline). International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2013.

29 EMA. Guideline on the limits of genotoxic impurities (EMEA/CHMP/QWP/251344/2006). Committee for Medicinal Products for Human Use (CHMP). European Medicines Agency; 2006.

30 WHO. Production of Zinc Tablets and Zinc Oral Solutions: Guidelines for Program Managers and Pharmaceutical Manufacturers. 2007.

31 WHO. Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report. Geneva, World Health Organization; 2002: Annex 11 (WHO Technical Report Series, No. 902).

32 WHO. Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth report. Geneva, World Health Organization; 2015: Annex 8 (WHO Technical Report Series, No. 992).

33 WHO. Good Pharmaceutical Practices, In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth report. Geneva, World Health Organization; 2016: Annex 1 (WHO Technical Report Series, No. 996).

***