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

\(^2\) 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>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Potential loss of state of control</td>
<td>Contamination risk</td>
</tr>
<tr>
<td>Biotech</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Liquids, sterile suspension/emulsion</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Liquids, sterile solution</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Metered dose inhalers, low and high API load*</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Powders, low API load</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Semisolids (ointment/cream), low API load</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Solid orals, modified release, low API load</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Transdermal</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Liquids, non-sterile suspension/emulsion</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Semisolids (ointment/cream), high API load</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Solid orals, modified release, high API load</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Solid orals, immediate release, low API load</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Powders, high API load</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Solid orals, immediate release, high API load</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Liquids, non-sterile solution</td>
<td>1</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 2. Classification of APIs according to the BCS

<table>
<thead>
<tr>
<th>Class</th>
<th>Solubility</th>
<th>Permeability</th>
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<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>

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. 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 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. 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*.

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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) website4. 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) website5 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 Pharmacopoeia, 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-PQT\(m\) 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

| 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 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>
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<td></td>
</tr>
<tr>
<td>List excipients that may affect bioavailability (BA)</td>
<td></td>
<td></td>
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<tr>
<td>Quantities provided of excipients that may affect BA? (Yes/No. If Yes, provide quantities)</td>
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<td></td>
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<tr>
<td>If tablets, are they coated?</td>
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<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>
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<tr>
<td>Storage conditions</td>
<td></td>
<td></td>
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<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>
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<td></td>
</tr>
<tr>
<td>May a biowaiver be possible for candidate product? (If yes, clarify briefly)</td>
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</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></td>
<td><strong>Active pharmaceutical ingredient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>Therapeutic index</td>
<td>All</td>
<td>If API is of narrow therapeutic index (NTI), score = 5</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>If API is potent, score = 3 (below 5 mg per dose)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>If API is highly potent, score = 5 (below 1 mg per dose)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Otherwise score = 1</td>
<td></td>
</tr>
<tr>
<td>A2</td>
<td>Genotoxicity</td>
<td>All</td>
<td>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.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>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).</td>
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<td></td>
<td></td>
<td></td>
<td>Otherwise score = 1</td>
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</tr>
<tr>
<td>A3</td>
<td>Monograph/specifications</td>
<td>All</td>
<td>If the API has a pharmacopoeial monograph, score = 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If the API is prequalified and/or has a CEP, score = 1</td>
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<td></td>
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<td></td>
<td>Otherwise score = 4</td>
<td></td>
</tr>
<tr>
<td>A4</td>
<td>Solubility</td>
<td>Solid dosage forms</td>
<td>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</td>
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<tr>
<td></td>
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<td></td>
<td>Otherwise for an API of BCS Class 2/4, score = 3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>If the API is of BCS Class 1 or 3, score = 1</td>
<td></td>
</tr>
<tr>
<td>A5</td>
<td>Hygroscopicity</td>
<td>Solid dosage forms</td>
<td>Highly hygroscopic to deliquescent, score = 3, hygroscopic score = 2, slightly or none score = 1</td>
<td></td>
</tr>
<tr>
<td>A6</td>
<td>Stability, storage and transport</td>
<td>All</td>
<td>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.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>If a shelf life (not retest period) is allocated, score = 3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>If retest period of ≥ 3 years at “room temperature” is allocated without special precautions, score = 1</td>
<td></td>
</tr>
</tbody>
</table>

*Continued*
### 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 | Biologies | 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 |  

**Excipients, including those that are removed during manufacture**

| 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 |  

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><strong>Finished pharmaceutical product</strong></td>
<td></td>
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</tr>
</tbody>
</table>
| F1 | Dosage format | 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 format 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, 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. | |

Continued
### 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

| Candidate product (INN, dosage form, strength): | Answer | Comments |
---|---|---|
Any aspect scoring 5 (not recommended) |
Any one or more scoring 4 or more (high risk) |
Any two or more scoring 3 or more (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


