Guideline on Reliance

For the National Medicines Regulatory Authorities of Ghana, Liberia, Sierra Leone, and The Gambia

Updated December 2, 2022

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Guideline on Reliance on decisions, reports, or information from other national medicines regulatory authorities (NMRAs) or regional and international bodies, Version 1 (Updated December 2, 2022)

Draft written by GHPP PharmTrain-Project Team (BfArM, Germany)	March 2021
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Date of coming into effect	<DD Month YYYY>[4]

Comments should be provided using the template for submission of comments. The completed comments form should be sent to <as appropriate (NMRA's Email)>.

Keywords	reliance; recognition; national medicines regulatory authority (NMRA) [5]; reference institution (RI)

[1]Last day of relevant committee/board meeting.
[2]Date of publication on the NMRA public website/1st day of the month following adoption of the guideline.
[3]Last day of the month concerned.
[4]First day of coming into effect. At latest 3 months after adoption.
[5] To be identified here during preparation of the guideline - keywords represent an internet search tool - Rapporteurs to propose and Working Party/Committee to adopt.

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Guideline on Reliance on decisions, reports, or information from other national medicines regulatory authorities (NMRAs) or regional and international bodies, Version 1 (Updated December 2, 2022)

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Style notes for this draft version:

[ ] Comments to be removed with finalization

< > Placeholder to be filled with (NMRA) specific information or to be decided if kept or deleted.

Acknowledgements

We duly thank the World Health Organization (WHO), Health Canada, and Food and Drugs Authority (FDA, Ghana) for publishing their guidelines that contributed in several aspects relevantly to the development of this guideline.

Executive summary

The development of this guideline is based on the outcomes and consensus of the meetings convened in January / February 2020 by GHPP-PharmTrain Project team of the Federal Institute for Drugs and Medical Devices (BfArM, Germany) with participants from the national medicines regulatory authorities (NMRA) of Liberia (LMHRA, Liberia Medicines and Health Products Regulatory Authority), Sierra Leone (PBSL, Pharmacy Board of Sierra Leone), and The Gambia (MCA, Medicines Control Agency).

This document has been discussed and adapted in exchange between LMHRA, PBSL, The Gambia MCA, Ghana (FDA, Food and Drugs Authority) and the GHPP-PharmTrain project team from March 2021 to November 2021.

From January 2022 the Joint Technical Working Group for Guidelines in Marketing Authorization (TWG-MAG), with the above-mentioned members, was established to continue the successful development of regulatory guidelines.

<This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance.>

1. Introduction (background)

The legal provision <quote title of national medicines Act if applicable> mandates the <NMRA> to regulate the importation, distribution, and manufacture of all medicinal products in <country>. The term “medicinal products” in the context of this TWG-MAG guideline includes finished pharmaceutical products (FPPs), biotherapeutics and vaccines.

NMRAs face an increasingly complex regulatory environment, with limited resources and a need to avoid duplication by communicating, collaborating, cooperating and forming coalitions to ensure product quality, safety and efficacy, as well as supply-chain security.

To this end, <NMRA> is permitted to take into account and give significant weight to assessments performed and decisions made by another regulatory authority or trusted institution, or to any other authoritative information in reaching its own decision. Using reliance on the expertise and regulatory outcomes of recognized reference institutions (RI) facilitates and accelerates national registration processes.

Available assessment and inspection reports of reference institutions in addition to the registration dossiers, assure NMRAs of the positive benefit-risk of a product and its identical quality with the product already approved elsewhere, while allowing them to reflect their own judgement on the benefit-risk balance as it relates to their specific country situation and the legislation in place. This contributes substantially to savings in regulatory resources, improvements in the quality of regulatory decisions and faster availability of needed therapies for patients.

Of note, <NMRA> remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions, assessments and information of other reference institutions.

1.1. Objectives

This guideline describes the prerequisites and information requirements of an application (for marketing authorization or variation) for a medicinal product that has previously been approved by reference institutions.

The objectives of this guideline are to provide guidance and clarification to applicants, including sponsors and industry, on how <NMRA> relies on foreign decisions, reports and information, in the assessment of medicinal products describe the practical steps for <NMRA's> regulators and applicants to effectively and efficiently implement and conduct the assessment activities using reliance on decisions, reports, or information from other NMRAs or regional and international bodies.

The <NMRA> reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to adequately assess the safety, efficacy or quality of a medicinal product. <NMRA> is committed to ensure that such requests are justifiable and that decisions are clearly documented.

All final decisions on the approval of marketing authorization or variation of medicinal products will be made by <NMRA>.

2. Scope

This guideline provides guidance to applicants and <NMRA's> regulators on the requirements and process for the registration/approval of medicinal products in <country> that have been approved by a recognized reference institution. For details on the reference institutions see section 5 and **Annex I**.

By using the approach of reliance, <NMRA> maximizes the efficiency in using their own resources. Moreover, <NMRA> is able to focus on value-adding activities. In addition, the burden of duplication of work done by reference institutions and duplication of work for applicants/manufacturers is reduced.

This guideline covers initial registrations/approvals and variations/post approval changes.

3. Legal basis

[This guideline has to be read in conjunction with of Part XY Section XY of the <NMRA> Act <year>. ***Choose as appropriate****.]*

This guideline is coherent with national/regional frameworks and policies. The usage of reliance by <NMRA> is supported/embedded in the <quote title of the regulation, if applicable>.

4. Assessment activities

NMRAs have several options for organizing their assessment activities.

In addition to a **full review**, there exist two reliance-based approaches to organize the assessment activities; verification or abridged/abbreviated review/regulatory pathway.

Verification is an administrative process to reach a regulatory decision, based on registration or authorization by a reference institution. The NMRA formalizes its decision by approving the product or submission and ensures the product for local registration and marketing. The NMRA does not undertake any own assessment activity. This may apply to full submissions or parts thereof (see 'Definitions' for details on full and partial reliance). Verification is applied where conformity with requirements of the reference institution is sufficient to meet the requirements of <NMRA>.

Abridged/abbreviated review is the assessment of suitability of use under local conditions and regulatory requirements, while relying partly or fully on prior assessment and inspection outcomes as well as Quality Control (QC) laboratory reports from the reference institution to inform the local decision (see 'Definitions' for details on abridged/abbreviated procedure).

5. Reference institutions

Regulatory authorities and regional and international bodies that are considered reference institutions by <NMRA> for the purpose of reliance/use of relevant decisions, reports or information are stated in **Annex I** (see also "Definitions" for clarification).

6. Dossier requirements

<NMRA> has published guidance documents and policies to assist applicants in the preparation and filing of medicinal product dossiers, for example, the common technical document CTD guideline (see reference list). Applicants should refer to the <NMRA> website for applicable guidance documents.

<NMRA should add their CTD Guideline in the reference list below>

This section provides guidance on the documentation specifically required for applying partial or full reliance mechanisms, as detailed in section 4.

6.1. Documentation Requirements

The format of the documentation should correspond to the CTD in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) format/content.

Currency of the documentation, i.e. the sameness of the contents of the application with the documentation available and underlying any regulatory decision of the reference institution is mandatory (see section 6.2).

6.1.1. For marketing authorization applications

A full dossier (CTD format) should be submitted including:

1. Module 1, regional administrative information, adapted, following the contents/format/structure laid out in **Annex II** ("Proposed documentation for the abridged procedure for reference institution-approved medicinal products").
2. Module 2, summaries, complete as submitted to the reference institution.

   Note: In the case of generic medicinal products for which a Clinical summary is not available, the Clinical overview (Module 2.5) should be included.
3. Module 3, quality documentation, as submitted to the reference institution, unless indicated otherwise according to the requirements of <NMRA>. If climatic zone III–IV stability data are not available, the commitment and protocol should be provided for stability studies under the appropriate climatic conditions for <country>. Any preliminary data under the required climatic conditions for <NMRA> should be provided. The stability data will be assessed by the reference institution, where applicable or possible.

   Additional country-specific information for Module 3 should be provided, as detailed in **Annex XX**.

   <can be deleted if not applicable, otherwise requirements have to be formulated in Annex XX>

4. Module 4, non-clinical documentation, <to be provided.> <to be provided on request.> in addition to summary in module 2.
5. Module 5, clinical documentation, (in addition to summary in module 2).

   For innovative medicinal products <to be provided.> <to be provided on request.>

   For generic products, complete documentation on bioequivalence studies should be provided in the submission in line with the TWG-MAG Guidelines on BE, Version 1, Updated 02 December 2022 to establish interchangeability and applicable national regulatory requirements for participating NMRAs.

6.1.2. For applications for variations

1. Module 1, adapted, following the contents/format/structure laid out in **Annex II** ("Proposed documentation for the abridged procedure for reference institution-approved medicinal products").
2. Module 2, complete as submitted to the reference institution.

   Note: In the case of generic medicinal products for which a Clinical summary is not available, the Clinical overview (Module 2.5) should be included.
3. Modules 3, 4 and/or 5 as submitted to the reference institution for the substantiation of the applied variation.

6.1.3. Additional information for marketing authorization applications as well as for applications for variations

1. All review(s), assessment reports as well as inspection reports by the reference institution, substantiating the current authorization status of the medicinal product, should be provided by the applicant when the submission is filed with <NMRA>.
2. Written confirmation of permission for sharing reference institution-owned non-public information with <NMRA> national regulatory authority (see **Annex III**).

   Note for variation applications: If the confirmation has been obtained for the initial marketing authorization application with unlimited validity, the confirmation does not have to be renewed with the reference institution. Nonetheless, the written confirmation should be part of each submission.

The legal information accompanying the dossier should be duly certified and authenticated under the procedure, in effect, in the country of origin, and issued by the appropriate entity.

3. Samples of the medicinal product from commercial batches, submitted to support the application as per sample schedule.

6.2. Requirements for Verification

The applicant should verify the “sameness” of the reference institution-approved medicinal product with the one applied for the purpose of reliance.

For this,

1. the “Quality information summary” (QIS) has to be provided (in CTD-module 1.2). Details on the information requested for finished pharmaceutical products (FPP) and for biologicals/biotherapeutic products (BTP) are provided in **Annex IVa** (QIS-RI-FPP) and **Annex IVb** (QIS-RI-BTP), respectively.
2. the applicant should confirm in writing that the review(s) provided is/are complete and unaltered. The applicant should confirm that the documentation filed in the submission is identical to that, on which the review(s) and authorization decision was based. If it is not identical, all differences should be clearly indicated.
3. the product should have been registered, prequalified and/or granted marketing authorization and is, in the latter case, actually on the market of the reference authority.

6.3. Requirements for abridged/abbreviated review

The abridged/abbreviated review may pertain to the full submission or parts thereof, depending on the suitability of use under local conditions and regulatory requirements.

An abridged/abbreviated review for **parts of the submission** may be applied for the active pharmaceutical ingredients (API). <NMRA> recognizes the Certificates of suitability to the monographs of the European Pharmacopoeia (CEP) for API as well as the Confirmation of API Prequalification (CPQ) issued by the WHO Prequalification Team Medicines Programme (WHO-PQ) for APIs as a validation of the quality of a certain API.

For an abridged/abbreviated review of the **full submission**, in addition to the documentation/information requirements laid out in sections 6.1 and 6.2 of this guideline a so-called bridging report should be submitted by the applicant.

The bridging report:

The reference institution’s assessments may not always account for specific circumstances that can significantly affect the benefit-risk of a medicinal product in other countries/regions. Hence, the reference institution’s assessment reports may have to be considered incomplete, when a reference institution-approved product is submitted for the regulatory approval in <country> and the conditions of use or the benefit–risk profile of the medicinal product may differ. In these cases, the applicant should support the application by providing evidence of a positive benefit–risk profile for the proposed conditions of use in <country>.

Differences in target population, epidemiology and other features of the disease, concomitantly used medicinal products and hence the interaction potential, local treatment and diagnostic modalities, and other factors can substantially affect the benefit-risk profile of a medicinal product. There can also be issues related to certain quality parameters, especially in relation to the stability under different climatic conditions.

A bridging report should, in particular, justify the:

- comparability of the studied population to the target population (e.g. ethnicity, gender representation, age groups) as regards demonstration of efficacy and safety;
- relevance of reference institution-approved conditions of use as regards epidemiology and disease pattern in <country> as well as other implications for efficacy and safety, e.g. feasibility of monitoring and precautionary measures (e.g. resistance testing or therapeutic drug monitoring);
- interactions with food and with other medications relevant in < country> that are not discussed in the reference institution's assessment report;
- therapeutic role of a product and its recommended use according to relevant national and international treatment guidelines;
- quality issues, including but not limited to, storage conditions and conditions of administration and use;
- risk management plan for a new drug (see 'Definitions' for details).

Provision of a bridging report is not mandatory, but may substantially facilitate conduct of the regulatory assessment, reduce the number of potential regulatory questions and shorten the duration of the regulatory approval process. This report has to be dated and signed by the author and the author's CV be attached.

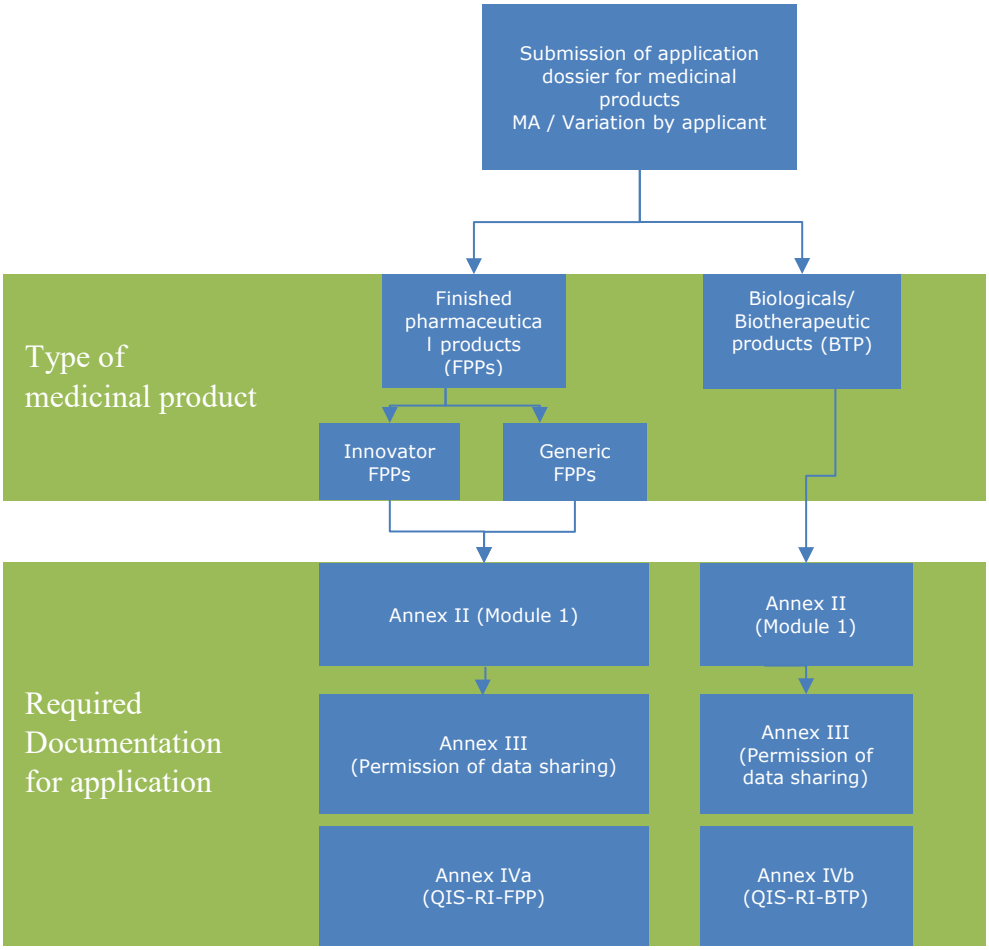

Figure 1: Version 1

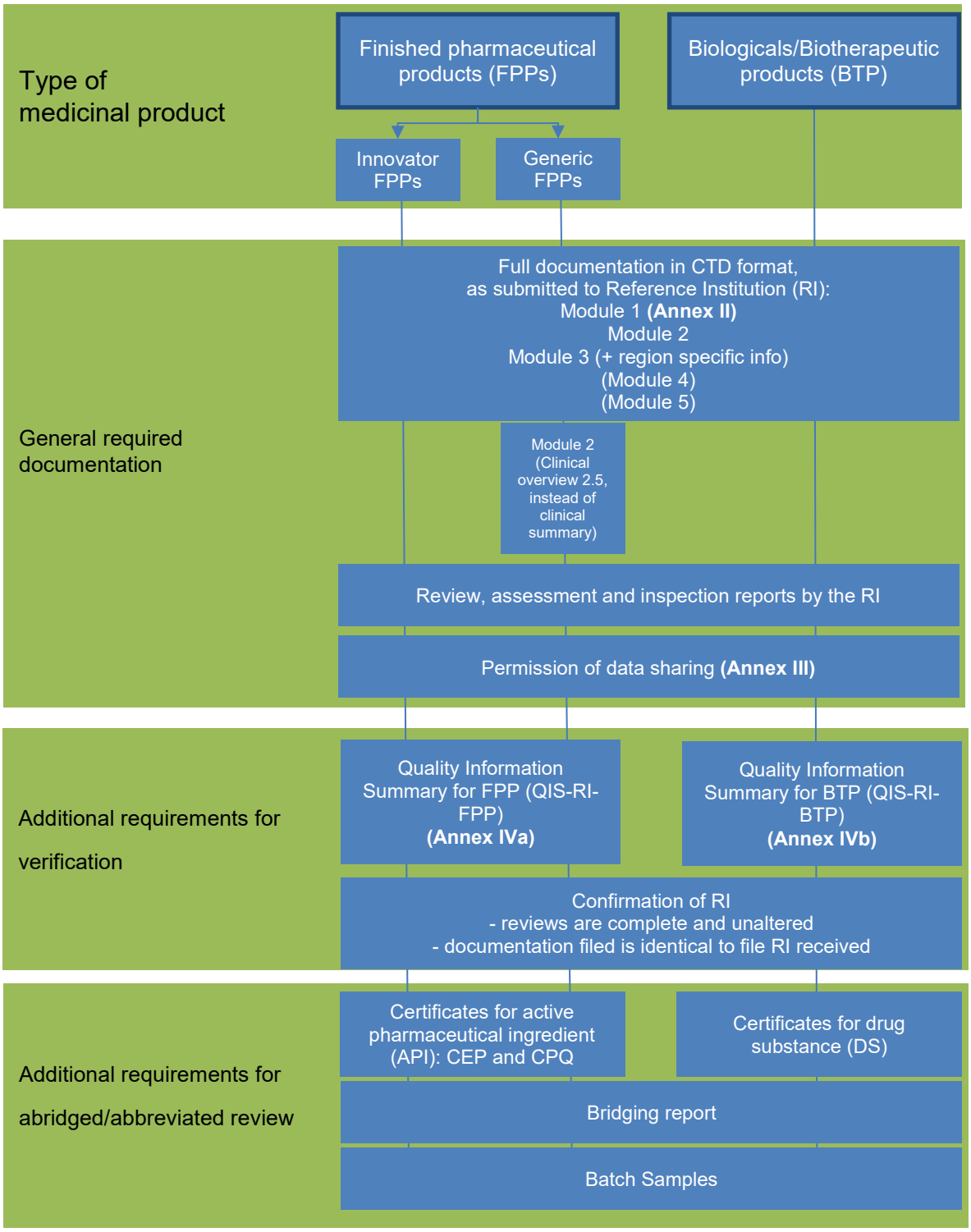

Figure 1: Version 2

Figure 1: Documentation requirements in reliance-based approach for the application of marketing authorization/registration or variations of medicinal products provided by the applicant.

<The NMRA should choose between Version 1 or 2 of Figure 1 for their GL and delete the other.>

7. Guidance for Implementation

7.1. Guiding Principles

<NMRA> adheres to the following guiding principles when using reference institutions' reviews:

1. <NMRA> uses, where appropriate, reference institutions' reviews to perform part of the evaluation or to inform <NMRA> s decision-making. However, <NMRA> does grant (or refuse to grant) a marketing authorization or approve a variation based solely on the existence of a reference institution's review and its corresponding regulatory decision.
2. The use of reference institutions' reviews may be applicable, to variable degrees, to the regulatory review of medicinal products covered under the scope of this guideline and when available, are considered when determining the review strategy. However, an applicant will not be required to file a submission at a reference institution, nor will <NMRA> unilaterally decide to delay the <country's> review until a reference institution's review is available.
3. The extent to which a reference institution's review may be used to inform <NMRA>'s regulatory decision on a medicinal product will be guided by <NMRA>'s estimation of the benefits and risks/limitations of using that review (or components thereof) to inform the <country's> regulatory decision-making process.
4. The NMRA reserves the right to subject all submissions for approval to an 'abridged' evaluation of a certain part of the application (e.g. relevant to use under local condition), such as product quality data in relation to climatic conditions and distribution infrastructure and a benefit-risk assessment in relation to use in the local ethnic population, medical practice/culture and patterns of disease and nutrition.
5. While the use of reference institutions' reviews may enhance timely access to high quality medicinal products, it is essential that benefit-risk assessments of health products be made within the context of the <country's> health care system. Final regulatory decisions on the granting or refusal or approval of a marketing authorization or variation of medicinal products for the citizens are made by <NMRA>.
6. In all cases, the <country's> product labelling (e.g. package insert, summary of product characteristics, patient information leaflet) will be reviewed by <NMRA> to ensure it meets <country's> requirements, in accordance with the Food and Drug Regulations, applying <NMRA> standard operating procedures and current practices.

7. Confidentiality of submitted data and non-disclosure to a third party is assured by the relevant national legislation and organizational measures applied by <NMRA>.

7.2. Timelines

Formal deficiencies in the submitted application and the dossier will be communicated to the applicant, in line with the national practice. Timelines for decisions from <NMRA> as well as clients' response timelines are detailed in <**Annex XX**>.

7.3. Reliance Principles for variations

NMRAs are encouraged to establish alternative accelerated timelines for variations on medicinal products that have previously been approved by the other NMRAs. Accordingly, those NMRAs should create a list of the NMRA approvals they will recognize. As an expedite regulatory pathway the following approaches of accelerated timelines could be established:

- The NMRA recognizes the decision of other regulatory authorities and does not perform a review of supporting data but is informed of the change. Using this approach, NMRAs could allow changes to be implemented immediately after receipt of the change notification.
- The NMRA performs an assessment of the decision of the NMRA of the licensing country to determine if recognition of the latter NMRA's decision is appropriate. Using this reliance-based approach, NMRAs established abbreviated review timelines (for details see <**Annex XX**>).
- The NMRA performs a partial review and evaluation of a complete supporting data package, as originally submitted to the licensing country. Using this approach, timelines would be expected to be shorter than the timelines of a common approval of variation.

If a variation application is rejected by <NMRA>, this will be communicated to the applicant with an explanation for the rejection. As appropriate, there should be an opportunity for dialogue between the <NMRA> and the applicant, as necessary, with the aim of resolving the NMRA's concerns with the application.

Withhold/Suspension/Withdrawal of the product as authorized by the reference authority (or from the list of prequalified products) must be reported by the marketing authorization holder (MAH) to the <NMRA> within 30 days including official document stating the reason for this action. When applicable, this should be a letter/document issued by the reference authority.

Definitions

Abridged review / abbreviated regulatory pathway / review

Regulatory procedures facilitated by reliance, whereby a regulatory decision is solely or partially based on application of reliance. This usually involves some work by the national regulatory authority (NMRA) that is practising reliance. It is expected that use of reliance in these pathways will save resources and time as compared with standard pathways, while ensuring that the standards of regulatory oversight are maintained.

Applicant

A person or entity who has applied for regulatory approval of a product or a change thereof. All applicants are to own the product. Representatives of product owners may not hold themselves as applicants unless they own the product.

In some jurisdictions this term is used in a wider sense (see “Marketing authorization holder)”.

Drug Product (DP)

A finished dosage form, for example, a tablet, capsule or solution that contains an active pharmaceutical ingredient, generally, but not necessarily, in association with inactive ingredients. Reference: Manufacturing, Processing, or Holding

Is synonymous to finished pharmaceutical product but specific for biotherapeutic products.

Finished Pharmaceutical Product (FPP)

Product that has undergone all stages of production, including packaging in its final container and labelling. An FPP may contain one or more active pharmaceutical ingredients.

Innovator finished pharmaceutical product

A novel medicinal product, which was the first product authorized for marketing by any country (normally as a patented product) on the basis of documentation of efficacy, safety and quality according to requirements at the time of the authorization.

Marketing Authorization Holder (MAH)

A person or entity whose product has been authorized by a national medicines regulatory authority to be on the market.

Medicinal products

Any substance or combination of substances prepared, sold or presented for use in the diagnosis, treatment, mitigation or prevention of disease, disorder of abnormal physical state or the symptoms of it or restoring, correcting or modifying organic functions in human beings

The term “medicinal products” in the context of this TWG-MAG guideline includes finished pharmaceutical products (FPPs), biotherapeutics, and vaccines. Not included are medical devices, in-vitro diagnostics, blood products and animal products.

Multisource (generic) finished pharmaceutical products

Is a medicinal product, which has the same qualitative and quantitative composition in active pharmaceutical ingredients and the same pharmaceutical form as the authorized reference medicinal product and which bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

National Medicines Regulatory Authority (NMRA)

A National medicines regulatory authority is a country’s entity responsible for the registration, marketing authorization, and other regulatory functions concerning medicinal products.

New Drug

New drug: a generic copy of an innovator product, that has not been previously registered as a pharmaceutical or biological product in <Country> or which has been marketed in <Country> for a period of not more than ten (10) years or any other period to be determined by the authority from time to time, for public health reasons.

Package

A box, packet or any other article in which one or more primary containers of medicinal products is or are to be enclosed in one or more other boxes, packets or articles

Patient Information Leaflet (PIL)

A leaflet in every pack of medicine containing information on the medicine for the user, such as patients.

Recognition

The acceptance of the regulatory decision of another regulator or other trusted institution. Recognition should be based on evidence of conformity that the regulatory requirements of the reference regulatory authority are sufficient to meet the regulatory requirements of the relying authority. Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement

Reliance (full and partial)

The act whereby the National Medicines Regulatory Authority (NMRA) in one jurisdiction may take into account and give significant weight to assessments performed by another NMRA or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others. Full reliance means that the authority relies on the entire assessments/inspection and quality control reports performed by another regulatory authority. Partial reliance means that the authority relies on certain documents/parts of the assessments performed by another regulatory authority, while for the other part(s) an independent, full assessment of the documentation submitted by the applicant is conducted.

Reference institution / Reference Regulatory Authority

An authority or institution which assessment and its outcome serve as basis for regulatory reliance. As per WHO guidance (https://www.who.int/news/item/29-04-2021-who-publishes-new-guidance-to-promote-strong-efficient-and-sustainable-regulatory-systems) this encompasses different levels of reliance.

In this document this term relates to a list of authorities/institutions determined by the NMRA including the transitional WHO listed authorities referred to as group B+C (https://www.who.int/publications/m/item/list-of-transitional-wlas) and WHO Prequalification Programme.

See also **Annex I** for clarification.

Summary of Product Characteristics (SmPC)

A document describing the properties and the officially approved conditions of use of a medicine; summaries of product characteristics form the basis of information for healthcare professionals on how to use the medicine safely and effectively

Variation

A variation is a change to the terms of a marketing authorisation. There are different types of variations with different regulatory requirements and procedures. For more detail for regulatory and procedural guidance proceed to <Guideline on variations XX>.

References

<NMRA should add their CTD Guideline in the reference list below>

WHO. Good Reliance Practices (GReP), Annex 11, 55th report of the World Health Organization Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP), WHO Technical Report Series No. 1033, 2021.

WHO. Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities, Annex5. World Health Organization, WHO Technical Report Series No. 986, 2014.

WHO. Good practices of national regulatory authorities in implementing the collaborative registration procedures for medicinal products, Annex 6. World Health Organization, WHO Technical Report Series No. 1019, 2019.

WHO. Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities, Annex 11 (Appendix 3B, 4, 5). World Health Organization, WHO Technical Report Series, No. 1010, 2018.

WHO. Template: Quality Information Summary (QIS) of the Biotherapeutic Product Approved by Stringent Regulatory Authority (SRA) (QIS-SRA). June 2018 https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwjcr5OGoqT0AhWiQvEDHaBLCSoQFnoECA4QAQ&url=https%3A%2F%2Fextranet.who.int%2Fpqweb%2Fkey-resources%2Fdocuments%2Fwho-trs-1010-annex-11-appendix-4&usg=AOvVaw0Qd4TjGX1ERAsiU7OBV6oN (Access of website: November 2021)
Reference is made to the WHO "Guidelines on submission of documentation for the pilot procedure for prequalification of rituximab or trastuzumab approved by stringent regulatory authorities" (Access of website: November 2021)

WHO. Annex 6 Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability Republication of Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability, WHO Technical Report Series, No. 992, Annex 7 with a new Appendix 2, 2017.

FDA Ghana. Guidelines for Registration of World Health Organization (WHO) Pre-Qualified Biological Products. FDA/SMC/BPU/GL-WPP/2013/03. Published by the Food and Drugs Authority of Ghana. Date of Issue: 2013/04/01.

FDA Ghana. Reliance Policy. FDA/GEN/POL-02. Published by the Food and Drugs Authority of Ghana. Date of Issue: 2nd January, 2019.

Health Canada. The Use of Foreign Reviews by Health Canada. Draft guidance document. Published by authority of the Minister of Health. Draft Date: 2012/09/11.

Collaboration, Not Competition: Developing New Reliance Models - Regulatory Collaboration. Exchange of Assessment Reports (ARs) with Regulators outside the European Union (EU). World Health Organization, WHO Drug Information Vol. 30, No. 4, 2016.

This guideline template is based on the structure of the harmonized Guideline on Guidelines V1, February 2021 developed by the joint working group of Food and Drugs Authority (FDA, Ghana), Liberia Medicines & Health Products Regulatory Authority (LMHRA, Liberia), Medicines Control Agency (MCA, The Gambia), Pharmacy Board of Sierra Leone (PBSL, Sierra Leone), and the Global Health Protection Programme (GHPP) PharmTrain-Project of the Federal Institute for Drugs and Medical Devices (BfArM, Germany)

List of Annexes

Annex I _List of reference institutions

Annex II_Documentation abridged procedure

Annex III_Confirmation of data sharing

Annex IVa_QIS-RI-FPP

Annex IVb_QIS-RI-BTP

<Please add additional NMRA specific annexes to the list that are mentioned in the guideline>

Annex I: List of reference institutions

List of regulatory authorities and regional and international bodies that are acknowledged as reference institutions for the purpose of reliance on/use of relevant marketing authorization decisions, reports or information

The following agencies/institutions/organizations classified as group B and C as per WHO framework https://www.who.int/initiatives/who-listed-authority-reg-authorities are assigned as reference institutions:

- European Medicines Agency (EMA)
- the National Medicines Regulatory Authorities (NMRA) of 27 Member States of the European Union (EU) and 3 EU associated states of the European Economic Area (EEA) (EU: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden; EEA: Iceland, Liechtenstein, Norway)
- Medicines and Healthcare Products Regulatory Agency (MHRA (UK))
- U.S. Food and Drug Administration (US-FDA)
- Pharmaceuticals and Medical Devices Agency (PMDA (Japan))
- Swissmedic (Switzerland)
- Health Canada
- Therapeutic Goods Administration (TGA (Australia))
- World Health Organization (WHO (Prequalification Programme))
- African Vaccine Regulatory Forum (AVAREF)
- Economic Community of West African States/West African Health Organization (ECOWAS/WAHO)
- Ghana Food and Drugs Authority (Ghana FDA)

Reliance on a regulatory decision based in itself on reliance should not be acceptable.

The basis for reliance should be an assessment of major parts of the submission.

Partial reliance for Active Pharmaceutical Ingredient (API) assessment to WHO (Certificate of a Pharmaceutical Product (CPP)), WHO Prequalification Team - Medicines (PQTm) (Confirmation of Prequalification (CPQ)) or European Directorate for the Quality of Medicines and Healthcare (EDQM) (Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP)) is acceptable.

Table of partial to full reliance approaches:

No reliance	Partial reliance	Work sharing	Full reliance
Any other application	WHO-PQ[1] (no CRP[2])	ECOWAS/WAHO	WHO-PQ (CRP)
	EMA MoUs[3] with Ghana FDA		EU-M4all[4] Swissmedic-MAGHP[5] MoUs[3] with Ghana FDA
	NMRAs: EU+EEA, UK, US, CH, CA, AU, JP		AVAREF
	US-FDA PEPFAR[6]		WHO EUL
	EDQM (CEP), WHO PQTm (CPQ), WHO (CPP)		

[1]: Prequalification
[2]: Collaborative Registration Procedure
[3]: Memorandum of Understanding
[4] previous EMA Article-58
[5]: Marketing Authorization for Global Health Products Procedure
[6]: U.S. President's Emergency Plan for AIDS Relief

This list of reference institutions is based on the WHO approach on the framework for evaluating and publicly designating regulatory authorities as transitional WHO-Listed Authority https://www.who.int/initiatives/who-listed-authority-reg-authorities

Annex II: Documentation abridged authorization procedure

Proposed documentation for the abridged authorization procedure for reference institution (RI)-approved medicinal products

All documents requested in the following adapted Module 1 MUST submitted as original and translated in English (notarized), if original is not in English

Adapted Module 1

	Documentation to be provided	**Comments**
1.0 Letter of application		Cover letter in English
Attachments to the letter:		
Annex III (permission of data sharing) of the abridged authorization procedure		
1.1 Comprehensive table of contents (TOC)	Comprehensive TOC including Module 1 information	
Quality information summary (QIS-RI-FPP (Annex IVa) and QIS-RI-BTP (Annex IVb))	Any differences in the dossier submitted to the RI should be explained, including differences in product information.	Submitted in English
1.3 Product information		
1.3.1 summary of product characteristics	Product information for the health care professional as applicable for the region where the application will be submitted.	Submitted in English
1.3.2 Patient information leaflet or package leaflet	Mock-ups	Submitted in English
1.3.3 Labelling	Mock-ups	Language and information to reflect national requirements
1.4 Marketing authorization from reference institution		
1.4.1 Marketing authorization from reference institution	Yes	

	Documentation to be provided	Comments
1.4.2 Assessment report from RI (Access to the full assessment report from the reference institution, if available)	Agreement from the manufacturer to allow reference institution to share the report with NMRAs. Prior to sharing, the reference institution and manufacturer should agree on the content of the document that is shared. If fully justified, sentences referring to highly confidential information and/or highly sensitive data and/or not related to the product assessment data could be masked.	Note that this type of document is available only for products registered in Europe, via the Centralized Procedure. Public reports are preferred as they already contain all useful information, except those considered to give a competitive advantage. .
1.5 Good manufacturing practices (GMP) certification		
1.5.1 Copy of the GMP certificate of the active pharmaceutical ingredient (API)/drug substance (DS) supplier, if available	Yes	Currently, this is not always available. If not available, statement signed by qualified person (QP) from FPP/DP manufacturing site to be provided or at least CoA
1.5.2 Copy of the GMP certificate of the finished pharmaceutical product (FPP) /drug product (DP) manufacturer(s)	Yes	
1.5.3 GMP inspection report of the manufacturing site(s) (FPP) from any reference institution	Agreement from the manufacturer to allow the reference institution to share the report with the NRA. Prior to sharing, the reference institution and manufacturer should agree on the content of the document that is shared. If fully justified, sentences referring to highly confidential information and/or highly sensitive data and/or not related to the product assessment data could be masked.	Public reports are preferred as they already contain all useful information, except those considered to give a competitive advantage.

	Documentation to be provided	Comments
1.6 Other documentation		
If generic dossier: – full GCP inspection report of the bioequivalence study from any reference institution, if any; – bridging report (where applicable) especially for innovative medicinal products (Section 6.3 in the Guideline on Reliance); – information on local representatives or distributor.	Agreement from the manufacturer to allow reference institution to share the report with NMRA. Prior to sharing, the RI and manufacturer should agree on the content of the document that is shared. If fully justified, sentences referring to highly confidential information and/or highly sensitive data and/or not related to the product assessment data could be masked.	Public reports are preferred as they already contain all useful information, except those considered to give a competitive advantage.
1.7 Others -Samples	Statement that samples have been submitted or, exceptionally, commitment letter for sample submission.	If, for a specific reason, samples cannot be submitted with the application, these should be submitted within two weeks after receipt of the submission.

Annex III: Confirmation of data sharing

Manufacturer's request for reference institution's (RI) permission for sharing RI-owned non- public information with <NMRA>

Date:_____*dd/mm/yyyy* _____

<manufacturer>

RE: Request to <RI> for a permission to <manufacturer> to share <RI>'s non-public information concerning <Product> with <NMRA>.

Dear <reference institution>,

<Manufacturer> as a <Marketing Authorization Holder> of the <RI> authorized <Product>, hereby requests the <RI's> permission to share <RI>-owned non-public information concerning <Product> for the purpose of the procedures of verification or abridged/abbreviated review and accelerated national registration of medicinal products based on reliance on recognized reference institutions.[6]
The information to be shared consists of

<RI> final GxP inspection reports for Product <date; version>;

<RI> Product assessment reports; and

<RI> <other, please specify> documents/reports that may be needed in the context of this Procedure.

The information will be shared with the <NMRA(s)>.

Yours sincerely,

Name: _____
Title: _____
RI: _____
Address: _____
Email: _____
Telephone number: _____
cc:

_____

[6] Reference to Guideline and Annex I

Annex IVa: QIS-RI-FPP

Quality Information Summary Of The Finished Pharmaceutical Product Approved By The Reference Institution (RI) (QIS-RI-FPP(crp))

A. Pharmaceutical product subject to RI collaborative procedure

A1. Reference Institution (RI)	
A2. Product registration/authorization number assigned by the RI	
Information as currently approved by the RI	
A3. Proprietary name of finished pharmaceutical product (FPP) in the RI country/region	
A4. Innovator or multisource (generic) FPP	
A5. Name of the holder of the RI marketing authorization and official address	
A6. International Nonproprietary Name (INN) of active pharmaceutical ingredient(s) (API(s)), including form (salt, hydrate, solvate, etc.)	
A7. Dosage form and strength	
A8. Product description (as in Product information, e.g. white, film-coated, capsule- shaped tablets debossed with “X” and score line on one side and plain on other side)	
A9. Primary and secondary packaging material(s) and pack size(s) (all pack types)	
A10. Storage conditions (as in Product information)	
A11. Shelf life of FPP (including in-use periods, where applicable)	
A12. Names of all approved manufacturers of FPP, physical address(es) of manufacturing site(s) (and unit if applicable), including intermediates, primary packaging site and release testing (indicate function of each site)	
A13. FPP storage conditions and duration over which stability, as reported to the RI, was established (e.g. 30 ± 2 °C/75 ± 5% RH for 24 months, 40 ± 2 °C/75 ± 5% RH for 6 months):	
Long-term (real time in months)	
Intermediate (duration in months)	
Accelerated (duration in months)	

B. Information that is considered confidential

Information as currently approved by the RI					
B1. Names of all approved API manufacturers, physical address(es) of manufacturing site(s) (and unit if applicable), including intermediates, contractors and release testing (indicate function of each site)					
B2. Active pharmaceutical ingredient master file/drug master file (APIMF/DMF version number(s) and date(s), if relevant					
Name of API	API manufacturer	APIMF/DMF version number(s) and date(s)			
B3. API specifications of the FPP manufacturer					
Standard (e.g. BP, Ph.Eur., Ph.Int., USP, in-house)[a]					
Specification reference number and version					
Test	Acceptance criteria	Analytical procedure (type/source/version)			
Description					
Identification					
Impurities					
Assay					
Others, please specify					
B4. API container closure system and re-test period					
Container closure system	Storage statement	Re-test period[b]			
[a] BP: British Pharmacopoeia; Ph.Eur: European Pharmacopoeia; Ph.Int.: The International Pharmacopoeia; USP: United States Pharmacopeia. [b] Indicate if a shelf life is proposed in lieu of a retest period (e.g. in the case of labile APIs).					
B5. FPP composition (formulation) information					
Component and quality standard	Function	Unit composition		Batch composition (largest approved size)	
		Quantity per unit or per mL	%	Theoretical quantity/batch	%
<complete with appropriate title, e.g. core tablet, contents of capsule, powder for injection>					
Subtotal 1					
<complete with appropriate title, e.g. film-coating>					

Subtotal 2					
Total					
Batch size in number of units, where applicable					
Additionally approved batch sizes - in number of units or kg, where applicable (add as many rows as necessary)					
Composition of all components purchased as mixtures (e.g. colorants, coatings, capsule shells, imprinting inks):					
B6. FPP manufacture					
Master production document reference number and version					
B7. FPP specifications					
Standard (e.g. BP, Ph.Int., USP, in-house)[a]					
Specification reference number and version/ effective date					
Test	Acceptance criteria (release)	Acceptance criteria (shelf life)	Analytical procedure (type/source/version)		
Description					
Identification					
Impurities					
Assay					
Others, please specify					

B8. Pharmacokinetic/safety/efficacy-related information used for RI approval of multisource products. Indicate:		
Type of study	*"X" in appropriate box*	Comparator product
Bioequivalence		
BCS-based biowaiver		
Other (specify)		
No study		
Notes/clarifications		

[a] BP: British Pharmacopoeia; Ph.Eur: European Pharmacopoeia; Ph.Int.: The International Pharmacopoeia; USP: United States Pharmacopeia.

B9. List of variations pending in the RI up to the date of verification		
Variation number	Variation	Type of variation according to RI regulations

B10. Discussion of differences between national application and data approved by the RI		
Deviation reference no.	Data submitted for national registration which deviates from data approved by the RI presented above. Mention also deviations in content of Product information, especially those related to indications, contraindications and posology.	Explanatory note

C1. Confirmation of content and verification by the RI		
Date of completion by the applicant	Name of person representing the applicant who completed the QIS-RI	Position in the organization
Date of verification by the RI *Part B10 is exempted from verification*	Person representing the RI who verified the QIS-RI information	Position in the organization

Change history to QIS-RI (crp) and Product information	
Date of revision (reported variation[a])	Description of revision/variation

[a] Variations approved by the RI after national registration of the FPP and affecting only the QIS-RI and/or Product information should be reported in the change history.

Annex IVb: QIS-RI-BTP

Quality Information Summary (QIS) of the Biotherapeutic Product Approved by a Reference Institution (RI) (QIS-RI-BTP)

A1. Biotherapeutic Product (BTP) or corresponding Similar Biotherapeutic Product (SBP) information (as currently approved by RI)

A1-1. Product reference number (RI number)
A1-2. Reference institution
A1-3. Name of the holder of the Marketing Authorization and official address
A1-4. Proprietary name of the drug product (DP) in the RI country/region
A1-5. International Nonproprietary Name (INN) of drug substance (DS)
A1-6. Dosage form and strength
A1-7. Description of the DP (as in Product Information, e.g. powder for concentrate for solution for infusion; concentrate for solution for infusion, white powder, clear, colourless liquid, excipients)
A1-8. Description of the DS. Brief description of the molecular features (e.g. engineered mouse/humanized/fully human monoclonal antibody, type of IgG), brief description of the manufacturing process (producing cell line, purification methods, presence of viral inactivation steps, etc.)
A1-9. Primary and secondary packaging material(s) and pack size(s) (all pack types)
A1-10. Storage conditions (as in Product Information) and any special precautions for storage (including storage conditions after reconstitution/first opening, where applicable)
A1-11. Shelf-life of the DP (including in-use period and conditions, where applicable)
A1-12. Names of all approved manufacturers of DP, physical address(es) of manufacturing site(s) (and unit if applicable), including intermediates, primary packaging site and release testing (indicate function of each site)
A1-13. Names of all approved DS manufacturers, physical address(es) of manufacturing site(s) (and unit if applicable), including intermediates, contractors and release testing (indicate function of each site)

A2. Reference Biotherapeutic Product (RBP) information (as approved by the RI at the time of submission of the SBP application)

A2-1. Product reference number (RI number), if applicable
A2-2. Reference institution
A2-3. Name of the holder of the Marketing Authorization and official address
A2-4. Proprietary name of the drug product (DP) in the RI country/region
A2-5. INN of DS
A2-6. Dosage form and strength
A2-7. Description of the DP (as in Product Information, e.g. powder for concentrate for solution for infusion; concentrate for solution for infusion, white powder, clear, colourless liquid, excipients)

A2-8. Description of the DS. Brief description of the molecular features (e.g. engineered mouse/humanized/fully human monoclonal antibody, type of IgG), brief description of the manufacturing process (producing cell line, purification methods, presence of viral inactivation steps, etc.)
A2-9. Primary and secondary packaging material(s) and pack size(s) (all pack types) if available
A2-10. Storage conditions (as in Product Information) and any special precautions for storage (including storage conditions after reconstitution/first opening, where applicable)
A2-11. Shelf-life of the DP (including in-use period and conditions, where applicable)
A2-12. Names of all approved manufacturers of DP, physical address(es) of manufacturing site(s) (and unit if applicable), including intermediates, primary packaging site and release testing (indicate function of each site) if available
A2-13. Names of all approved DS manufacturers, physical address(es) of manufacturing site(s) (and unit if applicable), including intermediates, contractors and release testing (indicate function of each site) if available
A2-14. References/source of information with corresponding URL addresses (e.g. labelling, EU SmPC, EPAR – Scientific Discussion, PMDA Review reports, FDA Chemistry review, scientific literature…)

BTP or corresponding SBP information (as currently approved by the RI) that will not be made publicly available

B1. Composition (formulation) information					
Component and quality standard	Function	Unit composition		Batch composition (largest approved size)	
		Quantity per unit or per mL	% (if applicable)	Theoretical quantity/ batch	% (if applicable)
<complete with appropriate title, e.g., active ingredients, excipients>					
Batch size in number of units/L, where applicable					
Additionally approved batch sizes - in number of units or L, where applicable (add as many rows as necessary)					
Excipients with known effects if applicable					

RBP information (as currently approved by the RI) that will not be made publicly available

B2. Composition (formulation) information (Applicable for a SBP submitted for prequalification)			
Name of the RBP			
Component and quality standard	Function	Unit composition	
		Quantity per unit or per mL	% (if applicable)
<complete with appropriate title, e.g., active ingredients, excipients>			

Excipients with known effects if applicable			

B3. BTP drug product specifications			
Standard (e.g. International Pharmacopoeia, British Pharmacopoeia, United States Pharmacopeia) if available			
Specification reference number and version/effective date			
Test	Acceptance criteria (release)	Acceptance criteria (shelf-life)	Analytical procedure (type/source/ version)
Visual appearance			
Identity			
Potency			
Impurities			
Endotoxin			
Sterility			
etc.			

B4. Pharmacokinetic/safety/efficacy related information used for RI approval of the SBP. Indicate: (Applicable for a SBP submitted for prequalification)		
Name of the RBP		
Name of the holder of the marketing authorization of the RBP		
Type of study		"X" in appropriate box
Comparability exercise/similarity exercise (head-to-head) comparability studies with the SBP in order to show similarity in terms of	quality	
	safety/non-clinical	
	efficacy/clinical	
Other (specify) (e.g., pharmaco-toxicological assessment, design of the use of pharmacodynamic markers, pharmacovigilance studies potentially performed, extrapolation of safety and efficacy)	-	
	-	
	-	
Notes/clarifications		

B5. Contact information for communication with RI	
Contact person and postal address	
(International code) Telephone number	
(International code) Fax number	
Email address	

Change history to QIS-RI and product information

Date of preparation of original QIS-RI: ……

Date of revision (reported variation*)	Revision/variation description

* Variations approved by the RI after prequalification of the Drug product and affecting only the QIS-RI and/or Product Information should be reported in the change history.