13th Invitation to Manufacturers to Submit an Expression of Interest (EOI) for Product Evaluation by the WHO Expert Review Panel (ERP) for Reproductive Health Medicines
12 October 2017

1. Background

In 2011, UNFPA's Executive Board approved a new Quality Assurance Policy for Reproductive Health Medicines. The preferred approaches are for procurement of finished pharmaceutical products (FPPs) that meet the following criteria:

1. FPPs prequalified by the WHO Prequalification Programme or authorized for use by a Stringent Drug Regulatory Authority (SRA)[1]; or
2. FPPs recommended for use based on advice provided by the Expert Review Panel for Reproductive Health Medicines (ERP/RHM).

2. Expert Review Panel for Reproductive Health Medicines

The ERP/RHM is an independent technical body composed of external technical experts and hosted by the Unit of Regulation of Medicines and other Health Technologies (RHT) of WHO Department of Essential Medicines and Health Products (WHO/EMP/RHT). The Procurement Services Branch of UNFPA (UNFPA/PSB) provides the Secretariat for the ERP/RHM. The ERP/RHM will be convened by WHO/EMP/RHT and review product dossiers submitted by manufacturers of FPPs that are not yet WHO-prequalified or SRA-authorized, undertake a quality risk analysis associated with the use of those products and provide written advice to the Secretariat to help making evidence based procurement decisions.

3. Eligibility criteria for ERP/RHM review

FPPs are eligible for review by the ERP if the following conditions have been met:

(a) the manufacturer of the FPP has submitted an application for prequalification of the product[2] by the WHO Prequalification Programme or provides written commitment to submit an application within three months from the date of approval into the ERP, and/or

(b) the manufacturer of the FPP has submitted an application for marketing authorization to an SRA, and it has been accepted for review by the SRA, and

[1] Stringent Regulatory Authority (SRA) means a regulatory authority (in case of the European Union both EMEA and national competent authorities are included) which is:

a) a member of ICH prior to 23 October 2015, namely: the US Food and Drug Administration, the European Commission and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency; or
b) an ICH observer prior to 23 October 2015, namely: the European Free Trade Association, as represented by Swissmedic and Health Canada; or
c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement prior to 23 October 2015, namely: Australia, Iceland, Liechtenstein and Norway.

For more information:
https://extranet.who.int/prequal/sites/default/files/documents/75%20SRA%20clarification_February2017_0.pdf

[1] Kindly note that the product submitted/to be submitted to the PQP or for SRA marketing authorisation must be from the same manufacturing site as the one submitted to the ERP process.

(c) the FPP is manufactured at a site that is compliant with the standards of Good Manufacturing Practice (GMP) that apply for the relevant product formulation (as verified after inspections by parties such as, but not limited to, SRA, WHO Prequalification Programme or any inspectorate participating in the Pharmaceutical Inspection Cooperation Scheme (PIC/S).

4. Reproductive health medicines 13th *Invitation for EOI for ERP for RH Medicines*

Interested manufacturers are encouraged to submit documentation for recommended dosage forms and strengths, as specified below, of reproductive health medicines in the following categories:

Treatment of maternal syphilis and prevention of congenital syphilis

Adult formulations

- Benzathine benzylpenicillin 2.4 million units per dose in vial for reconstitution and intramuscular Injection

5. Basis of review process

The ERP will assess the ERP dossier. Risk assessment is based on the following major product attributes of submitted products:

Risk assessment is based on the following major product attributes of submitted products:

- GMP status of the manufacturing site(s)
- API source and quality
- FPP manufacturing process and FPP quality specifications
- Stability data
- Evidence of safety and efficacy (e.g. bioequivalence data)

6. Time limitation

If the ERP issues a positive opinion, any subsequent recommendation for procurement by UNFPA with regard to an FPP will be valid for a period of no more than 18 months ("validity period"), or until the FPP is WHO-prequalified or SRA-authorized, whichever is the earlier. However, the Secretariat may, in its sole discretion, request the ERP to consider extending the validity period for up to an additional 12 months if the FPP is not yet WHO-prequalified or SRA-authorized within the validity period. UNFPA may refer more than one request for such an extension to the ERP and in this case a new ERP dossier has to be submitted. Any advice from ERP with regard to extension of the validity period will be based on ERP's evaluation of the new dossier and progress of the FPP dossier in the PQP or SRA pipeline.

7. How to submit an EOI

In order to submit an Expression of Interest for product evaluation, the manufacturer must submit the following:

- A covering letter expressing interest to submit the product to ERP for review.
- A letter about submitting/accepting the dossier for assessment from the WHO Prequalification of Medicines Programme or an SRA confirming that the product application has been accepted for review OR A letter stating commitment to submit dossier for assessment to WHO PQT or an SRA within 3 months of results from ERP.
- Documentation related to the GMP status of the FPP manufacturer, i.e. evidence of GMP compliance issued by WHO PQP, SRA or PIC/S member regulatory authority and, if applicable,

manufacturer is strongly encouraged to submit inspection report even if the outcome may be negative.

- A completed questionnaire with annexes (attached, see Appendix 1: The Interagency Finished Pharmaceutical Product Questionnaire based on the model quality assurance for Procurement Agencies).
- A full set of the analytical test methods including Standard Test Procedures (If non-pharmacopeia).
- Two non-returnable product samples as requested in Section 1.7.1 of the questionnaire.
- Electronic copies of the submission.

All documentation must be provided in two formats:

- One digital copy (CD)
- One hard copy

Submissions should be addressed to the UNFPA office in Copenhagen, as follows:

UNITED NATIONS POPULATION FUND
United Nations City
51 Marmorvej
2100 Copenhagen
Denmark

REF: ERP for Reproductive Health Medicines, UNFPA/DNK/EOI/17/032
Attention: Seloi Mogatle

8. Deadline for submissions:

All submissions must reach the UNFPA reception in Copenhagen by Tuesday**, 31 October 2017, at 17.00h (Copenhagen time).**

9. Further information and contact details

Any questions related to the review processes should be addressed to Ms. Seloi Mogatle at mogatle@unfpa.org.

10. United Nations Global Marketplace

All the information in this document, as well as eventual clarifications, will be made public in the UNGM website (www.ungm.org).

Appendix 1

Interagency finished pharmaceutical product questionnaire

Interagency finished pharmaceutical product questionnaire[1]

[1] Working document as per WHO TECHNICAL REPORT SERIES, NO. 986 under Annex 3 -*Model quality assurance system for procurement agencies* -Appendix 6- *Interagency finished pharmaceutical product questionnaire based on the model quality assurance system for procurement agencies.*

Please fill out one separate form for each pharmaceutical product

Section 1: Administrative Section

1.1 Product identification

1.1.1 Active pharmaceutical ingredient(s) (use INN if any):

1.1.2 Generic name of the product:

1.1.3 Trade (proprietary) name (if any):

1.1.4 Dosage form:

☐ Tablets ☐ Capsules ☐ Injectable ☐ Syrups/oral liquids

☐ Other: (Please specify)

1.1.5 Strength per dosage unit:

1.1.6 Route of administration:

☐ Oral ☐ I.M. ☐ I.V. ☐ S.C. ☐ Other (Please specify)

1.1.7 Please provide the formulation of the product (complete qualitative and quantitative composition including active ingredient(s), overages if any and excipients). Please also indicate the standard for each ingredient (e.g. BP, USP, in-house). Mention specifically if the product is a fixed-dose combination (FDC) or co-packaged: **Annex A**

1.1.8 Please state inactive ingredients (excipients) of medical/pharmaceutical relevance, amount in dosage form or per dosage unit (e.g. contains alcohol 10%, paraben…….)

1.2 Packaging

1.2.1 Description and materials used for primary packaging[2] and pack size (quantity of dosage-form units per pack): **Annex B**

1.2.2 Description, pack size and material used for secondary packaging materials: **Annex C**

Contact details

1.3 Manufacturer identification

Name, address and activities of the manufacturer and manufacturing site(s) (or contract manufacturer(s):

Name of manufacturer, contract manufacturer if any	

[2] For example, HDPE bottle, Alu-Alu strip, neutral glass vial.

Reference of manufacturing licence, date and expiry date, if any	
Physical address. Please specify units, and block if existing	
Telephone number, facsimile number and email contact details	
Activity (e.g. packaging)	

1.4 Supplier identification

(to be filled in if not identical to that indicated in 1.3)

Name of company:
Physical address (complete details required):
Telephone number:

Fax:

Website:

Email:

Link with the product

☐ Marketing licence holder ☐ Manufacturer

☐ Distributor/wholesaler ☐ Other

1.5 Note for the applicant

Please note that the information in this questionnaire can be shared confidentially among ICRC, MSF, WHO procurement centre, UNFPA and UNICEF for procurement purposes. If you have any objection, please indicate this to the relevant agency that you are dealing with.

Has the dossier been submitted to any of the following: ERP, ICRC, MSF, WHO procurement centre, UNFPA, UNICEF?

☐Yes ☐No

Please indicate to which one:

Please provide the date of the submission:

1.6 Regulatory (licencing) status

1.6.1 In the country of manufacture. Provide a copy of the licence in **Annex D**

☐ Product registered and currently marketed
Licence no:

☐ Product registered for marketing in the country of manufacturing but currently not marketed
Licence no.:

☐ Product not registered *(please clarify)*:

- Please attach a certificate of pharmaceutical product (CPP) according to the WHO Certification Scheme (WHO Technical Report Series, No. 863; an earlier version is not acceptable) in **Annex E.**

- If a CPP cannot be obtained from the national medicines regulatory authority (NMRA), please state the reason and send an equivalent document if any.

- Submit recent as well as historical deficiency letters issued by the WHO Prequalification Programme (PQP)/SRA in relation to the specific product dossier in **Annex F**.

1.6.2 In other countries

List other countries where the product is registered and is currently marketed *(please provide registration number)*-Provide a copy of the licence-**Annex-D**

1.6.3 WHO prequalification status, if applicable

This product is prequalified by WHO/PQP.[3]

☐ Yes ☐ No

If yes, please attach a copy of the relevant WHO/PQP acceptance letter signed by your company in **Annex G**.

1.6.4 If submitted for prequalification: indicate date of submission, WHO acceptance letter for product dossier review mentioning the WHO reference number assigned by WHO for this specific product in **Annex H**

[3] WHO Prequalification website: http://apps.who.int/prequal/.

1.7 Samples for technical evaluation

1.7.1 Samples of finished product and insert information

You are required to provide a sample of the finished product(s) offered. If you cannot submit with the questionnaire, please state the reason and when you will do so:

1.7.2 Primary packaging label language (attach a copy in **Annex I**):

☐ Bilingual English/French ☐ English ☐ French

☐ Other (specify)

1.7.3 Secondary packaging label language (attach a copy in **Annex I**):

☐ Bilingual English/French ☐ English ☐ French

☐ Other (specify) ☐ Multilingual English/French/Spanish

For oral powder for suspension and powder for injection, in-use periods and storage conditions after reconstitution should be stated on the product label/leaflet.

1.7.4 Patient information leaflet/Package insert (attach a copy in **Annex J**)

☐ Yes ☐ No

Section 2: Active pharmaceutical ingredients

(If there is more than one active pharmaceutical ingredient or more than one API manufacturer is used, please replicate this section.)

2.1 Details of API used (INN if any)

2.1.1 Manufacturer

Manufacturer (name, physical address and country)/manufacturing site:

GMP certificate from the country of origin: attach a copy of the GMP certificate, if available, in **Annex K.**

Last inspection of API manufacturing site performed, when available (please attach GMP certificate or relevant letter) by:

☐ Finished product manufacturer

☐ WHO Prequalification Programme, Geneva

☐ EDQM

☐ US FDA

☐ PIC/S members

☐ Others (specify)

☐ None of above

Outcomes and date:

Is/are the API used to manufacture this product WHO-prequalified?

☐ Yes ☐ No

2.1.2 API specifications

☐ British Pharmacopoeia (BP) (edition/year):

☐ United States Pharmacopeia (USP) (edition/year):

☐ The International Pharmacopoeia (Ph.Int.) (edition/year)

☐ Others (specify):

Specifications additional to those in the pharmacopoeia referred to above if available

☐ Yes ☐ No

- Attach a copy of the FPP manufacturer internal API specifications in **Annex L**.
- If analytical methods are in-house, different from BP, USP and Ph.Int. attach a copy of the analytical method and analytical validation data in **Annex M.**

For sterile API:

Please provide the data on validation of the sterile aspects including recent media fill validation data, as applicable, in **Annex N**.

Describe the method of sterilization used when applicable:

2.1.3 Certificate of analysis

Please provide a copy of the certificate of analysis of the API from the API manufacturer as well as from the finished pharmaceutical product (FPP) manufacturer in **Annex O.**

2.1.4 Suitability of monograph for API

Are you in a possession of the Certificate of suitability to the monograph of the European Pharmacopoeia (CEP) for APIs?

☐ Yes ☐ No

Certificate of suitability to the monograph of the European Pharmacopoeia (CEP): please attach a copy of the CEP and its annexes in **Annex P1**.

Certificate No.:

2.1.5 Open part of drug master file (DMF) registered in (country):

Do you have a Technical file: ☐ Yes (please attach)-**Annex P2** ☐ No

Section 3: Finished pharmaceutical product

3.1 Manufacturing site GMP status

GMP inspections carried out by an NMRA

	NRA of country of origin	Any other inspection of PIC/S member	
GMP certificate no.			
Valid until			
Country			

Please attach the recent/valid GMP certificates/letter(s) of compliance in **Annex Q**

Other GMP inspections carried out by (include information for all that apply in the last 5 years):

Agency	Date of audit	Outcome
WHO Prequalification Programme		
UNICEF Supply Division		
MSF International		
ICRC		

Other (specify)		

3.2 Finished pharmaceutical product specification

Standard	Edition	Year published
BP		
USP		
Ph.Int.		
In-house	Year documented	
Specifications additional to those in the pharmacopoeia referred to above (e.g. dissolution, syringe ability) explain:		
Other (specify)		

Please attach copies of release and shelf-life specifications for the FPP in **Annex R**. If analytical methods are in-house, different from BP, USP and Ph.Int., attach a copy of the analytical method and analytical validation data in the same in **Annex R**.

Please attach a copy of the certificate of analysis for the three last batches released in **Annex S**.

3.3 Method of manufacture and process validation:

Have the manufacturing methods for each standard batch size been validated?

☐ Yes ☐ No

If no, please clarify:

If yes, please provide details of validation status in the table below:

The batch size of the validated batches (minimum, maximum size)	

The batch numbers of the validated batches	
Manufacturing dates of the validated batches	
Reference number for the process validation report	
If processes are yet to be validated, the reference number for the process validation protocol should be indicated	

Provide batch formulae for all proposed batch sizes:

- P l e a s e provide in **Annex T** a flow diagram and brief narrative describing the manufacturing and control process of this product with relevant parameters.

3.3.1 Additional information for sterile products

- Provide the data on validation of the sterile aspects of the product including recent media fill validation data as applicable in **Annex U**.

- Describe the method of sterilization used including conditions such as temperature , time, pressure, if applicable:

3.4 Stability of finished product

3.4.1 Is stability testing data available?

☐Yes ☐No

Please provide the protocol and the report for accelerated and long-term stability testing, including: type and material of container; conditions (temperature/ relative humidity/duration of stability study); number of batches involved in the study (minimum three); batch sizes for each lot tested; date of beginning of the study; and study conclusions. These can be provided in **Annex V**.

3.4.2 Was the stability testing done on a product of the same formula, same API source, manufactured on the same site and packed in the same packaging material as the product that will be supplied?

☐ Yes ☐ No

If no, describe the differences:

3.4.3 Please specify whether stability studies have been done or are ongoing with all declared API sources:

☐ Yes ☐ No

Submit a declaration in **Annex W** that stability studies have been done or are being done with all declared API sources.

If no, explain why:

3.4.4 Do you have ongoing stability data for this product?

☐ Yes ☐ No

Attach status report of any ongoing stability studies in **Annex X**.

3.4.5 Shelf-life as it appears on packaging:

☐ 2 years ☐ 3 years ☐ 4 years ☐ 5 years ☐ Other (please specify):

3.4.6 Specific storage conditions for this product as they appear on the packaging and based on stability studies (e.g. “Do not store above 30 °C – Protect from light”):

Temperature	
Light	
Humidity	
Other (specify)	

3.4.7 Product suitable for use in the following ICH Climatic Zones:

☐ Zone I

☐ Zone II

☐ Zone III

☐ Zone IVa

☐ Zone IVb

☐ Other (please specify):

3.4.8 For oral powder for suspension and powder for injection, or injection that may be further diluted, or multidose containers provide in-use stability data and storage conditions after reconstitution and/or dilution in **Annex Y**.

Indicate the period (hours/days) and storage condition until which the product is stable after reconstitution and/or dilution based on the available in-use stability data:

Section 4: Safety/efficacy and/or therapeutic equivalence

(WHO Technical Report Series (TRS), No. 902, Annex 11/ TRS No. 937, Annex 7 or recent version)

4.1 For innovator products

Please attach a summary of pharmacology, toxicology and efficacy of the product in **Annex Z**.

4.2 For generic products: therapeutic equivalence

☐ Demonstrated

☐ Not demonstrated

☐ Not relevant, please explain why

If demonstrated,

- Attach graphic/pictorial representation of summary study results in **Annex AA.**
- Provide a copy of the report of the proof of therapeutic equivalence (BE study) comparative dissolution profile, dissolution tests, and others, if any, in **Annex AB**.
- For bioequivalence studies, indicate the stringent regulatory authority (SRA)/ WHO/PIC/S inspection status of the Contract Research Organisation (CRO) (if the CRO has ever undergone inspections in relation to the current or other studies).

- Attach schematic representation of study design in **Annex AC**
- Attach study protocol summary in **Annex AD**

4.2.1 By in vivo bioequivalence studies

☐Yes ☐ No (explain):

Study period (dd/mm/yyyy): from to

Reference product

Generic name:	
Dosage form:	
Strength:	
Brand/trade name:	
Manufacturer:	
Manufacture site:	
Batch number:	
Expiry date:	

Study protocol

Contract research organization	
Country of study:	
Number of volunteers:	
Study design (describe in detail):	

Bio batch size:	
Bio batch number:	
Bio batch API(s) source(s):	
Study conclusion:	

Study results:

Study conclusion:

4.2.2 By comparative in vitro dissolution tests according to conditions described in WHO BCS classification document (WHO Technical Report Series, No. 937, or later)

☐Yes ☐ No (explain):

Reference product

Generic name	
Dosage form	
Strength	
Brand/trade name	
Manufacturer	
Manufacture site	
Batch number	
Expiry date	

Name and contact details of laboratory performing tests:

Study results
F2 (similarity factor) value (standard 50–100%):

F1 (difference factor) value:

Study conclusion:

4.2.3 By another method (please describe the method and the study conclusion, briefly):
☐Yes ☐ No (explain):

4.3 Commitment

The product used in the therapeutic equivalence study is essentially the same as the one that will be supplied (same materials from the same suppliers, same formula and same manufacturing method):

☐ Yes ☐ No

If no, explain what the differences are and justify that the differences do not have any impact on the bioavailability:

Section 5: Commitment and authorization

5.1 Commitment

I, the undersigned, (*position in the company, e.g. General Manager, Authorized Person, Responsible Pharmacist*), acting as responsible for the company *(name of the company)*, certify that the information provided (above) is correct and true,

(if the product is marketed in the country of origin, select the appropriate box below)

☐ and I certify that the product offered is identical in all aspects of manufacturing and quality to that marketed in (*country of origin*), including formulation, method and site of manufacture, sources of active and excipient starting materials, quality control of the product and starting material, packaging, shelf-life and product information.

☐ and I certify that the product offered is identical to that marketed in *(name of country)*, except:

(e.g. formulation, method and site of manufacture,
sources of active and excipient starting materials, quality control of the finished product and
starting material, packaging, shelf-life, indications, product information)

If any changes occur to the information after the submission of this product questionnaire, the manufacturer/supplier undertakes to provide the relevant update as soon as possible.

Date: Signature:

5.2 Power of attorney

The manufacturer authorizes a distributor to submit the questionnaire

Date: Signature:

Distributor (Signed by Distributor for Manufacturer under power of attorney)

Please provide a copy of the power of attorney in **Annex AE**.

5.3 Authorization for sharing information with other agency

I, the undersigned confirm that the company has no objection to the information contained herein being shared with the agencies listed in clause 1.5 except:

I, the undersigned, certify that the information provided above is accurate, correct, complete, up-to-date and true at the time of submission.

Full name:

Full title/position in company:

Company name:

Signature Date

Company seal/stamp:

Section 6: Attachments/annexes

Attachments or Annexes to the questionnaire should be in PDF format and should be well indexed to facilitate review

Please ensure that all documents necessary to enable objective evaluation of your product are attached. This checklist may not be exhaustive.

☐ A. Formulation of the product (complete qualitative and quantitative composition including active ingredient(s) and excipients (1.1.7)

☐ B. Description and composition of primary packaging materials (1.2.1)

☐ C. Description and composition of secondary packaging materials (1.2.2)

☐ D. Copy of product registration and market status– Licence No (1.6.1)

☐ E. Certificate of pharmaceutical product (CPP) according to the WHO Certification Scheme (WHO Technical Report Series, No. 863. An earlier version is not acceptable) (1.6.1)

☐ F. Recent as well as historical deficiency/acceptance letters issued by PQP/SRA in relation to the specific product dossier (1.6.1)

☐ G. Copy of the relevant WHO Prequalification acceptance letter signed by your company (1.6.3)

☐ H. WHO acceptance letter for product dossier review mentioning the WHO reference number assigned by WHO for this specific product (1.6.4)

☐ I. Copy of primary and secondary packaging/label (1.7.1)

☐ J. Patient information leaflet/package insert (1.7.4)

☐ K. GMP certificate of the API manufacturer(s) from the country of origin (2.1.1)

☐ L. Copy of the internal API(s) specification(s) (2.1.2)

☐ M. Validated analytical methods if analytical methods for API are in-house analytical method, different from BP, USP and Ph.Int. (2.1.2)

☐ N. Data on validation of the sterile aspects of the product including recent media fill validation data, as applicable (2.1.2)

☐ O. Copy of the certificate(s) of analysis of the API from the API manufacturer as well as from the FPP manufacturer (2.1.3)

☐ P1. Copy of the certificate of suitability to the European Pharmacopoeia (CEP) and its annexes (2.1.4)

☐ P2. Attach a copy of the Technical file (2.1.5)

☐ Q. Recent/valid GMP certificates/letter of compliance of the FPP manufacturer (3.1)

☐ R. If in-house specification is different from BP, USP and Ph.Int., attach copy of the in-house finished product specifications and also validated analytical methods (3.2)

☐ S. Copy of the certificate of analysis for the three last batches released (3.2)

☐ T. Flow diagram and brief narrative describing the manufacturing and control process of this product with relevant parameters (3.3)

☐ U. Data on validation of the sterile aspects of the product including recent media fill validation data as applicable (3.3.1)

☐ V. Protocol and report for accelerated and long-term stability testing (3.4.1)

☐ W. Declaration that stability studies have been done or are being done with all declared API sources (3.4.3)

☐ X. Status report of any ongoing stability studies (3.4.4)

☐ Y. In-use stability data and storage conditions after reconstitution for oral powder for suspension, powder for injection, or injection that may be further diluted, or multidose containers (3.4.8)

☐ Z. Summary of pharmacology, toxicology and efficacy of the product (4.1)

☐ AA. Graphic/pictorial representation of summary study results (4.2.3)

☐ AB. Copy of the report of the proof of therapeutic equivalence (BE study) comparative dissolution profile, dissolution tests, and others if any (4.3)

☐ AC. Schematic representation of study design (4.3)

☐ AD. Study protocol summary (4.3)

☐ AE. Copy of the power of attorney (5.2)