Invitation to Manufacturers of Amoxicillin Dispersible Tablets (DT) to Submit an Expression of Interest (EOI) for Product Evaluation by the WHO Expert Review Panel (ERP) for the UN Commission on Life-Saving Commodities for Mothers and Children
(20th May 2015)

1. Background

In 2010, the UN Secretary-General’s Global Strategy for Women’s and Children’s Health highlighted the suffering of women and children around the world caused by lack of access to life-saving commodities. The Global Strategy called on the global community to work together to save 16 million lives by 2015 through increasing access to and appropriate use of essential medicines, medical devices and health supplies that effectively address leading avoidable causes of death during pregnancy, childbirth and childhood. This challenge was taken up by the UN Commission on Life-Saving Commodities for Women and Children (the Commission), which is a part of the Every Woman, Every Child movement and has the overall goal to increase access to these commodities in the world’s poorest countries. The Commission has defined a list of 13 overlooked life-saving commodities for women and children; identified key barriers preventing access to and use of these commodities; and recommended innovative action to rapidly increase both access and use. Amoxicillin in dispersible tablet formulation has been identified as the key commodity for use in childhood pneumonia.

2. Amoxicillin DT for Childhood Pneumonia

Pneumonia is one of the leading causes of death in children in the developing world, killing around 1.4 million children under-five per year. The numbers of people who seek medical care with symptoms of pneumonia are astronomically low, and as a result the proper treatment of antibiotics is not received. Adequate access to antibiotic treatment within the first twenty-four hours of a suspected case of bacterial pneumonia is life-saving. In a recent review by the Child Health Epidemiology References Group (CHERG), it is estimated that community management of all cases of childhood pneumonia could decrease under-five mortality from pneumonia by 70%; thus potentially saving approximately 900,000 children under the age of five per year.

The WHO has established new recommendations for the treatment of childhood pneumonia for those under the age of 5. First-line treatment is now Amoxicillin (preferably in dispersible tablet form i.e. DT) given twice daily for 5 days. This has been defined in detail in the WHO’s Integrated Management of Childhood Illness: Caring for New-borns and Children in the Community Handbook and is in line with the new Community Health Worker Training Package from UNICEF and WHO.

3. Expert Review Panel for Amoxicillin Dispersible Tablets

In order to assure availability and procurement of quality amoxicillin dispersible tablets, the implementation strategy for the UN Commission on Life-Saving Commodities for Women and Children has included establishing an Expert Review Panel (ERP) for amoxicillin.

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1 WHO Priority Medicines for Mothers and Children (http://www.who.int/medicine/publications/A4prioritymedicines.pdf)
The ERP is an independent technical body composed of external technical experts and hosted by the Unit of Quality Assurance and Safety of Medicines of WHO’s Department of Essential Medicines and Health Products (WHO/QSM/EMP). UNICEF Supply Division will provide the secretariat for the ERP. The ERP will be convened by WHO/QSM and will review product dossiers submitted by manufacturers of amoxicillin dispersible tablets, undertake a quality risk analysis associated with the use of the product and provide advice to the Secretariat that can be used to make evidence based procurement decisions.

4. Eligibility Criteria for ERP Review

Finished pharmaceutical products (FPP) are eligible for review by the ERP if the following conditions have been met:
(a) The FPP is manufactured at a site that is compliant with the standards of Good Manufacturing Practice (GMP) that applies for beta lactams (as verified after inspections by parties such as Stringent Drug Regulatory Authority (SRA)\(^3\), WHO Prequalification Programme, any inspectorate participating in the Pharmaceutical Inspection Cooperation Scheme (PIC/S) or UNICEF) and,
(b) The product is registered or in the process of being registered in the country of origin (either for marketing or for export) or the product holds marketing authorization to a third party country.

5. Technical Specifications

Interested manufacturers are encouraged to submit documentation for the recommended dosage and strength, as specified here;

Amoxicillin 250mg and 500mg scored dispersible tablets, blister of 10 dispersible tablets. Target pack sizes are 10, 20 and 100 tablets.

The dispersible tablets should contain Amoxicillin Trihydrate equivalent to 250mg Amoxicillin complying with one of the pharmacopoeias:
- BP
- Ph.Eur.
- Ph.Int.
- USP (Amoxicillin)

The dispersible tablets should comply with one of the pharmacopoeias:
- BP general monograph for tablets and general notices
- Ph.Eur. general monograph for tablets and general notices
- Amoxicillin Tablets for Oral Suspension USP, general notices and requirements

A Patient Information Leaflet (PIL) should be included in each pack.

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\(^3\) Stringent Drug 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 the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH (as specified on its website); or
- b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by SwissMedic, Health Canada and World Health Organization (WHO) (as may be updated from time to time); or
- c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement including Australia, Norway, Iceland and Liechtenstein (as may be updated from time to time).
6. Product dossier and questionnaire documentation and requirements

The manufacturer shall provide a product dossier which provides the following information and complete the pharmaceutical product questionnaire which summarizes the information about:
- Product registration information;
- Regulatory (licensing) status of the FPP and manufacturing facility;
- finished product specifications and information regarding compliance with international quality (pharmacopoeias) standards, if available;
- Stability testing data (both accelerated and real time studies) as per ICH and/or WHO guidelines;
- Product labeling information;
- Active pharmaceutical ingredient (API) characteristics and certification; and
- Safety and efficacy data (e.g. Bioequivalence)

Guidance on conducting bioequivalence studies

Comparator product for amoxicillin dispersible tablets
Based on the assumption that the posology for the tablets in clinical use will include that they be dispersed in water prior to administration, it is recommended that proposed products be compared against Amoxil powder for oral suspension (GlaxoSmithKline) which is, for example, available in the UK or Clamoxyl powder for oral suspension (GSK) which is available in countries such as Spain, France, and Belgium. Please note it should be highlighted that comparators must be sourced from the market of an ICH-associated country as this assures the quality of the comparator.

Development of Bioequivalence study protocols
Guidance is available for the development of bioequivalence study protocols in general. Section 6 of the ICH Guideline for Good Clinical Practice - E6 describes the information that should be included in a clinical study protocol and adherence to this guideline is strongly recommended. The guideline is available on the ICH website at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1_Guideline.pdf

If bioequivalence data is not available at the time of the submission by Monday, 22 June 2015, manufacturers are requested to indicate when they expect the Bioequivalence study to be conducted and when the study report will be forwarded for the ERP. In such cases the submission to ERP should include multi-media comparative dissolution profile data employing an acceptable comparator product (see above).

7. Basis of review process

The ERP will assess the complete ERP dossier. 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)
8. Time Limitation

If the ERP issues a positive opinion, any subsequent recommendation for procurement with regard to a FPP will be valid for a period of no more than 12 months ("Validity period"). However, the Secretariat may, in its sole discretion, request the ERP to consider extending the Validity period for up to an additional 12 months. UNICEF 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.

9. How to Submit an EOI

In order to submit an Expression of Interest for amoxicillin dispersible tablets evaluation, the manufacturer must submit the following:
- A covering letter expressing interest to submit the product to ERP for review;
- Documentations related to the GMP status of the FPP manufacturer (example: evidence of GMP compliance issued by WHO PQP, SRA or PIC/S member regulatory authority or, if applicable, an inspection report).
- A completed Questionnaire with annexes (attached)
- A non-returnable product sample as requested in Section 12 of the Questionnaire.
- Electronic copies of the submission

UNICEF Supply Division will screen the submissions for completeness. Incomplete submissions will not be forwarded to the WHO ERP. All documentation must be provided in two formats: One digital copy (CD/USB) and one hard copy.

Submissions should be addressed to UNICEF Supply Division in Copenhagen, as follows:
UNICEF SUPPLY DIVISION
OCEANVEJ 10-12
2150 NORDHAVN
COPENHAGEN
DENMARK
REF: ERP Amoxicillin Dispersible Tablets
Attention: David Muhia and Henrik Nielsen

10. Deadline for Submissions:

All submissions must reach the UNICEF Supply Division in Copenhagen by Monday, 22 June 2015, at 17.00 hrs. (Copenhagen time).

11. Further Information and Contact Details

Any questions related to the review processes should be addressed to David Muhia (dmuhia@unicef.org) or Henrik Nielsen (hnielsen@unicef.org), keeping Adam Ali (aaali@unicef.org) in copy.

12. 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).