Prequalification of Medicines Programme

Dr Olexandr Polishchuk
Division of Health Systems and Public Health
WHO EURO
Copenhagen, Denmark
apo@euro.who.int

Developed by Dr Lembit Rägo
Coordinator
Quality Assurance and Safety: Medicines (QSM)
Department of Essential Medicines and Pharmaceutical Policies (EMP)
Geneva, Switzerland
Content

• PQP in short
• What can it offer?
• PQP – pediatric formulations prequalified
• Training
• Regulatory advise
• Technical assistance
• Conclusions
Prequalification of Medicinal Products: Objectives

- Propose a list of **prequalified products and manufacturers** meeting international norms and standards of which the quality, efficacy and safety has been assessed, inspected and controlled.

- Ensure that **international norms and standards** are applied at all the steps of the Prequalification Programme.

- Make sure re-evaluation and **maintenance** of the list are performed and that variations and changes are correctly controlled.

- Help the national drug regulatory authorities to build up capacity in **assessment, inspection and control** meeting international norms and standards.

- Develop the **local possibilities** of production and clinical studies by offering customized technical assistance.
Scope of medicines PQ

- Limited to priority essential medicines
- Published in invitations for Expression of Interest (EOI) on Prequalification website
- EOIs include medicines that have been identified by the respective WHO disease departments as vital to effective treatment and to expanding treatment programmes
PQP Structure

Coordinator: Lembit Rägo
QSM

Tony Gould
Programme Manager

Jacqueline Sawyer
Liaison Officer

Laura Oakes
Head of Secretaries

Milan Smid
Capacity Building/Training

Jitka Sabartova
Quality Control Labs

Andre van Zyl
Head of Inspections

Matthias Stahl
Head of Assessments

Secretaries

Inspectors

Assessors
Medicines Prequalification Process

Expression of Interest

Assessment
Additional information and data
Compliance

Inspections
Corrective actions
Compliance

Product dossier SMF

Prequalification

Monitoring
Handling of complaints
Dossier maintenance (variations)
PQ Programme components

• Evaluation of Quality, Safety and Efficacy of prioritised essential medicines
• Inspection of manufacturers and CROs
• Monitoring of the products after prequalification
• Prequalification of quality control laboratories
• Building capacity of regulators, manufacturers and quality control laboratories
Key outputs

• Published list of prequalified medicinal products
  – Used principally by UN agencies, including UNAIDS and UNICEF, and any other agency or organization involved in bulk purchasing of medicines, to guide their procurement decisions

• Published list of prequalified laboratories
  – The list may be used by any organization to ensure that testing for quality monitoring is done at an acceptable standard
Does PQ status make a difference?

Prequalified antimalarial medicines rarely fail QC testing whereas non-PQ products often do
(from total 3.6% vs. 39.7%; data from 2009/2010 study)
Paediatric products prequalified - dispersible tablets:

- Abacavir (as sulfate) 60mg
- Lamivudine/Nevirapine/Stavudine 60mg/100mg/12mg
- Lamivudine/Nevirapine/Stavudine 30mg/50mg/6mg
- Lamivudine/Nevirapine/Zidovudine 30mg/50mg/60mg
- Isoniazid/Pyrazinamide/Rifampicin 30mg/150mg/60mg
- Artemether/Lumefantrine 20mg/120mg
Products prequalified and under assessment

• To date 46 paediatric products have been prequalified
  – 38 Anti-HIV,
  – 3 Anti-TB,
  – 4 Anti-Malaria and
  – 1 Anti-Influenza

• 23 are under assessment (11 Anti-HIV, 5 Anti-TB, 6 Anti-Malaria and 2 Zinc products)
  – These products are categorized as paediatric based on their dosage form and/or strength. In a few cases tablet-divisibility was also taken as criteria (example Isoniazid 100mg tablets).
Paediatric products under assessment:

- Abacavir (as sulfate) 20mg/ml oral solution – 1
- Efavirenz 50mg tablets – 1
- Efavirenz 100mg tablets - 1
- Lamivudine 10mg/ml oral solution - 1
- Lamivudine/Stavudine 30mg/6mg tablets - 1
- Lamivudine/Stavudine 60mg/12mg tablets- 1
- Lamivudine/Zidovudine 30mg/60mg dispersible tablets - 1
- Stavudine 1mg/ml powder for oral solution - 1
- Zidovudine 50mg/5ml oral solution – 3

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- Isoniazid/Pyrazinamide/Rifampicin 30mg/150mg/60mg dispersible tablets - 1
- Isoniazid 100mg tablet - 2
- Isoniazid/Rifampicin 30mg/60mg tablets - 1
- Pyrazinamide 150mg tablets – 1

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- Amodiaquine (as HCL)/Artesunate 67.5mg/25mg tablets - 2
- Amodiaquine (as HCl)/Artesunate 135mg/50mg tablets - 2
- Artesunate/Mefloquine (as HCl) 25mg/50mg tablet - 1
- Artemether/Lumefantrine oral suspension – 1

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- Zinc (as sulfate) 20mg dispersible tablets - 2
PQ of SRA approved innovator and generic products

- Assessment and inspections by a stringent regulatory authority (SRA) are recognised
- SRAs are generally those in ICH regions and associated countries
- Abbreviated process for prequalifying medicines approved by a SRA
- Also limited to defined priority essential medicines
Transparency

• Assessment and inspection reports are published in response to a World Health Assembly resolution

• A WHO Public Inspection Report (WHOPIR) provides a summary of the inspection (where found to be GMP complaint)

• A Notice of Concern (NOC) is a letter reflecting areas of concern where the non-compliances require urgent attention and corrective action by the manufacturer or research organization.
Training

• Mostly for regulators and for local industries

• Variety of topics – both more general and very specific topics (see more on the PQP web site specific section)
PREQUALIFICATION PROGRAMME
A United Nations Programme managed by WHO

Vision
Good quality medicines for everyone.

Mission
In close cooperation with national regulatory agencies and partner organizations, the Prequalification Programme aims to make quality priority medicines available for the benefit of those in need.

This is achieved through its evaluation and inspection activities, and by building national capacity for sustainable manufacturing and monitoring of quality medicines.

Strategy

- Apply unified standards of acceptable quality, safety and efficacy.
- Comprehensively evaluate the quality, safety and efficacy of medicinal products, based on information submitted by the manufacturers, and inspection of the corresponding manufacturing and clinical sites.
- Prequalify quality control laboratories of pharmaceuticals.
- Build the capacity of staff from national regulatory authorities, quality control laboratories, and from manufacturers or other private companies, to ensure medicines quality.

Key output

The list of prequalified medicinal products used for HIV/AIDS, malaria, tuberculosis and for reproductive health produced by the Programme is used principally by United Nations agencies — including UNAIDS and UNICEF — to guide their procurement decisions. But, the list has become a vital tool for any agency or organization involved in bulk purchasing of medicines, be this at country level, or at international level, as demonstrated by the Global Fund to Fight AIDS, Tuberculosis and Malaria.
Training workshops

- Training workshops and seminars

  Training Workshop on Pharmaceutical Development with a Focus on Paediatric Formulations

  - **Beijing, P.R. China**
    21-24 June 2010
    [Details]

  Conference on Quality of Active Pharmaceutical Ingredients

  - **Beijing, P.R. China**
    29-31 March 2010
    [Details]

  Planning, conduct and regulatory assessment of stability studies

  - **Accra, Ghana**
    7-9 December 2009
    [Details]

  WHO Seminar for European Manufacturers and EU Holders of Marketing Authorizations

  - **Copenhagen, Denmark**
    26 November 2009
    [Details]

  Manufacture of sterile medicines - advanced training workshop for State Food and Drug Administration (SFDA) GMP inspectors

  - **Nanjing, P.R. China**
    16 - 20 November 2009
    [Details]

  WHO workshop on assessment of bioequivalence data submitted to regulatory authorities

  - **Kiev, Ukraine**
    26 - 30 October 2009
    [Details]

  Advanced Training Workshop on WHO prequalification requirements for Reproductive Health and Seminar for Indonesian Manufacturers on WHO Prequalification Programme

  - **Jakarta, Indonesia**
    [Details]
Participants in trainings organized or co-organized/supported by PQP

- **2007**
  - Others: 57
  - QCL staff: 103
  - Regulators: 198
  - Manufacturers: 165

- **2008**
  - Others: 68
  - QCL staff: 301
  - Regulators: 263
  - Manufacturers: 263

- **2009**
  - Others: 44
  - QCL staff: 49
  - Regulators: 396
  - Manufacturers: 396

- **2010 I-VI**
  - Others: 8
  - QCL staff: 84
  - Regulators: 168
  - Manufacturers: 263
Pharmaceutical Development

Training Workshop on Pharmaceutical Development with focus on Paediatric Formulations

Beijing, PR of China
Date: 21 to 25 June 2010

World Health Organization

INTERNATIONAL PHARMACEUTICAL FEDERATION

QUALITY MEDICINES FOR EVERYONE
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<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
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<tr>
<td>0800 - 0830</td>
<td>Registration of participants</td>
<td>NCPBP</td>
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<tr>
<td>0830 - 0900</td>
<td>Opening Ceremony and welcome address</td>
<td>- Li Yunlong Director-general (NCPBP)</td>
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<td>- Dr L Rago Coordinator (WHO)</td>
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<td>- Dr T Sam (FIP)</td>
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<td>- Representative from SFDA, P. R. China (TBA)</td>
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<td>Introduction of participants</td>
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<tr>
<td>Moderator</td>
<td>Dr AJ van Zyl</td>
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<tr>
<td>0900 - 0930</td>
<td>Introduction:</td>
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<tr>
<td></td>
<td>• The need for paediatric medicines: A WHO perspective</td>
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<td>• Essential medicines and paediatric dosage forms</td>
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<td>From neonates to adolescents:</td>
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<td>o Developmental physiology.</td>
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<td>o Paediatric pharmacokinetics and pharmacodynamics, toxicology</td>
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<tr>
<td>0930 - 1015</td>
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<td>Dr K Hoppu</td>
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<td>1015 - 1045</td>
<td>Tea</td>
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<tr>
<td>Moderator</td>
<td>Dr S Mills</td>
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<tr>
<td>1045 - 1115</td>
<td>Biopharmaceutical Classification System (BCS)</td>
<td>Dr L Rago</td>
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<tr>
<td>1115 - 1200</td>
<td>Ethical considerations in clinical trials</td>
<td>Dr K Hoppu</td>
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<tr>
<td>1200 - 1245</td>
<td>Bio availability and bio equivalence studies in paediatrics</td>
<td>Prof JM Aiache</td>
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<tr>
<td>1245 - 1345</td>
<td>Lunch</td>
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<tr>
<td>Moderator</td>
<td>Dr AJ van Zyl</td>
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<tr>
<td>1345 - 1415</td>
<td>Pharmaco-vigilance and safety of medicines in children</td>
<td>Dr L Rago</td>
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<tr>
<td>1415 -1600</td>
<td>CASE STUDY</td>
<td>Dr K Hoppu</td>
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<td>Prof JM Aiache</td>
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<tr>
<td>Moderator</td>
<td>Dr B Schmauser</td>
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<tr>
<td>0900 - 0945</td>
<td>Dosage form design and manufacture (Tablets, capsules, syrups etc)</td>
<td>Prof P York</td>
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<tr>
<td>0945 - 1030</td>
<td>Scientific principles: Excipients, colorants, flavours, and active pharmaceutical ingredient properties</td>
<td>Dr S Mills</td>
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<td>Moderator</td>
<td>Dr B Schmauser</td>
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<tr>
<td>1045 - 1130</td>
<td>Selection of packaging materials</td>
<td>Dr S Mills</td>
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<tr>
<td>1130 - 1200</td>
<td>Practical problems in developing Fixed Dose Combinations and bilayer tablets</td>
<td>Industry representative (Guilin)</td>
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<tr>
<td>1200 - 1230</td>
<td>Practical problems in developing Fixed Dose Combinations and bilayer tablets</td>
<td>Industry representative (Holley)</td>
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<td>1230 - 1330</td>
<td>Lunch</td>
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<td>Moderator</td>
<td>Mr S Mallyya</td>
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<tr>
<td>1330 - 1400</td>
<td>Suitable dosage forms for paediatrics</td>
<td>Prof JM Aiache</td>
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<tr>
<td>1400 - 1600</td>
<td>CASE STUDY</td>
<td>Prof P York</td>
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<td>1600 - 1615</td>
<td>Tea</td>
<td>Dr S Mills</td>
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<td>Moderator</td>
<td>Prof P York and Dr S Mills</td>
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<tr>
<td>1615 - 1715</td>
<td>PRESENTATION OF CASE STUDY OUTCOME AND DISCUSSION</td>
<td>Groups</td>
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Tuesday 22 June 2010
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<th>Time</th>
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<tr>
<td></td>
<td>Moderator: Mr S Mallya</td>
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<tr>
<td>0900 - 0945</td>
<td>Introduction to development pharmaceutics</td>
<td>Dr S Mills</td>
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<tr>
<td></td>
<td>• Laboratory batches, pilot batches, full-scale batches</td>
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<td>• Definitions and purpose</td>
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<td>• Scale-up issues</td>
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<td>• Packaging</td>
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<td>Setting (tentative) acceptance criteria for manufacturing process validation</td>
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<tr>
<td>0945 - 1015</td>
<td>Industry perspective on practical approaches and experiences in development pharmaceutics</td>
<td>Industry representative (Novartis)</td>
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<tr>
<td>1015 - 1045</td>
<td>Industry perspective on practical approaches and experiences in development pharmaceutics</td>
<td>Industry representative (Desano)</td>
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<td>1045 - 1100</td>
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<td>Moderator: Dr B Schmauser</td>
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<tr>
<td>1100 - 1145</td>
<td>Selecting and developing an appropriate paediatric dosage form using a Quality by Design approach</td>
<td>Dr T Sam</td>
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<tr>
<td>1145 - 1230</td>
<td>Stability testing of APIs and finished products.</td>
<td>Mr S Mallya</td>
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<td>1230 - 1330</td>
<td>Lunch</td>
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<td>Moderator: Mr S Mallya</td>
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<tr>
<td>1330 - 1415</td>
<td>Analytical Method Development</td>
<td>Dr B Schmauser</td>
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<td></td>
<td>• Originator and multisource generic FPPs</td>
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<td>• Specifications</td>
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<td>• Stability</td>
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<td>• Parallel development of analytical methods for cleaning validation</td>
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<td>1415 - 1600</td>
<td>CASE STUDY</td>
<td>Dr S Mills</td>
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<td>Dr T Sam</td>
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<td>Moderator: Dr AJ van Zyl</td>
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<tr>
<td>0900 - 0945</td>
<td>Introduction to the Prequalification of Medicines Programme.</td>
<td>Dr A J van Zyl</td>
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<tr>
<td>0945 - 1030</td>
<td>Applications for prequalification: Dossier requirements</td>
<td>Mr S Mallya</td>
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<tr>
<td></td>
<td>- Multisource (generic) products</td>
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<td>- Products from ICH regions</td>
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<td>- New products that are not considered as &quot;Innovators&quot; or &quot;Generics&quot;</td>
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<tr>
<td>1030 - 1115</td>
<td>Inspections in Prequalification (Including GMP and GCP)</td>
<td>Dr A J van Zyl</td>
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<td>1115 - 1130</td>
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<td>Moderator: Dr AJ van Zyl</td>
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<tr>
<td>1130 - 1215</td>
<td>Dossier maintenance (including variations)</td>
<td>Dr B Schmauser</td>
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<tr>
<td>1215 - 1300</td>
<td>Questions and Answers</td>
<td>All presenters</td>
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<td>1300 - 1400</td>
<td>Lunch</td>
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<tr>
<td>1400 - 1500</td>
<td>Workshop evaluation by participants</td>
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<td>1500 - 1600</td>
<td>Certificates and Closing</td>
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Regulatory advise

• Regulatory advise is provided by PQP for more complicated products
  – Design of bioequivalence studies, applicability of biowaivers etc.
  – Pharmaceutical development aspects
  – ...

QUALITY MEDICINES FOR EVERYONE
Technical Assistance

- Key objective: Facilitate prequalification of priority medicines
- Provision of consultants to advice on
  - GMP or GCP compliance
  - Data development and compilation of dossier
- Assistance is separated from the assessment / inspections
- Assistance may be followed by specific trainings
- Assistance is provided free of charge
Technical assistance
2006-2010 (I-VI)
What about safety?

• Do we need more emphasis on safety monitoring?
  – Tools are there but the question is what to do and when
Promoting Safety of Medicines for Children
WHO, 2007 (pp 1- 60)

- Text on the web as follows:
  www.who.int/entity/medicines/publications/essentialmedicines/Promoting_safe_med_childrens.pdf

- WHO Book Shop for orders:
  http://www.who.int/bookorders/anglais/detart1.jsp?sesslan=1&codlan=1&codcol=15&codcch=705
Norms and Standards

- Guidelines and standards in the area of quality assurance for medicines apply also to the medicines for children.

- “Development of paediatric medicines: pharmaceutical development. Points to consider” (currently V.2 of Working document QAS/08.257).

- Quite a number of specific monographs for paediatric formulations in process and already adopted for inclusion in the international Pharmacopoeia. -->

Norms and Standards

- Challenge of oral dosage forms and diethylene glycol is addressed in the general pharmacopoeia text of oral liquids (Manufacture section)

- Additional communications for health professionals and NMRAs to be aware of this challenges are currently under development
Conclusions

• Paediatric formulations – priority for PQP

• Training, advise and assistance has been/and will be provided

• Can in cooperation with applicants facilitate achieving having more paediatric formulations prequalified
THANK YOU!

• Questions?