1. Rosemary Roberts, M.D.  
Director, Office of Counter-Terrorism and Emergency Coordination  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

General Comment:

The document lacks discussion of regulatory and manufacturing issues with respect to preferred pediatric dosage forms. The section on the bottom of page 7 of 15, "Desirable attributes of a paediatric dosage form" identifies some regulatory issues such as: minimum, non-toxic excipients; reliable administration; and flexibility/adaptability of the medicine to account for developmental and size differences, with the ability to reliably divide the unit dose. In addition, some manufacturing issues are identified such as: easily produced, stable in a variety of climates; palatable; and commercially viable. Many of these issues are noted in the Research Needs section.

Specific Comments:

1. Refer to pages 6-7, under Summary of Evidence, an interest in solid dosage forms over liquid: There was general acceptance of the benefits of solid dosage forms over liquid dosage forms for stability, dosing and administration issues....The need for a multidisciplinary and 'holistic' approach to paediatric medicines was highlighted and the potential of a 'platform' solid dosage form (e.g. granules or pellets) as a preliminary form providing flexibility for further processing into a range of alternative paediatric drug delivery systems was presented.

Comment: Later in the document, the report discusses the use of a flexible "platform," as if it is simple for a manufacturer to make some multipurpose granules that can easily be made into capsules or tablets or possibly a solution of whatever the necessary dosage strength is.

2. Refer to page 8, under End-users-needs: On the basis of these findings, it was suggested that interventions should be targeted at the levels of research and development, policy makers, manufacturers and procurement and logistics.

Comment: please clarify what end-user-needs means? What about the needs of the pediatric population?
3. Refer to page 9, under Proposed Recommendations, #1, 2nd paragraph:
Provided the product can be dispersed in breast milk from the mother, it could potentially be used in very young children (0-6 months). This type of product is feasible to manufacture in facilities that have conventional tableting facilities, but requires excipients that ensure stability and palatability. Examples of existing dispersible tablet products suggest that they can be more affordable than standard liquid dosage forms.

Comment: This is an interesting idea, but the discussion implies that if a manufacturer can make a tablet, then the same manufacturer can make something that dissolves in breast milk. The section does not mention whether the product is stable in breast milk or if the breast milk may interfere with absorption.

The section also does not discuss dispersing in infant formula. Perhaps that is included under “breast milk”? There are concerns about reconstituting formula with water in developing countries. In developing countries, do women have breast pumps readily available to get the milk for mixing with these medications?

4. Refer to page 10, #6 mentions transdermal patches drug delivery technology.

Comment: There could be some regulatory and manufacturing challenges with this delivery technology as the transdermal patches can be unreliable, in that patches may fall off, issues about covering patches, and what are appropriate locations to apply a patch during the various developmental stages of childhood. There are also safety issues with patches, such as children chewing on the patches, the caregiver applying a new patch because the other patch falls off – this may lead to toxic concentrations of drug absorbed for some products, such as fentanyl.

2. Catherine M. Wilfert, M.D.
   Senior Technical Advisor to CEO
   Elizabeth Glaser Pediatric AIDS Foundation
   Prevention of Mother-to-Child Transmission

   It is very general but appropriately places high priority on solidmeds which can be dosed appropriately.

3. Andrew E Mulberg, MD, FAAP, CPI
   Portfolio Leader, Internal Medicine, Established Products
   CNS/IM Late Development
   JPRD

   I would welcome the additional opportunity of participating in this critical discussion if possible. We have several current programs that interface here at J&J. I would love to see the presentations and literature if available to send in an easy manner.
***also see attached document with his additional comments/the materials he mentions

4. Phil Walson, MD  
*Visiting Professor, Dept Laboratory Medicine*  
*Georg-August-Universitat Medical School*

Thanks for sending me the draft. Did I miss it or did they forget to mention refrigeration, or lack of it, as a major issue in the developing world? Clean water was mentioned but only very briefly. Should have been another major issue. Good general overview of the problems despite these minor issues.

5. Stephen M. Tuel, M.D., MBA  
*President*  
*Zebra Pharmaceuticals, Inc.*

As a technical formulation document it is well done. There is mention of the need for clinical trials in the Outstanding Issues section, but the key issues of regulatory reform, liability protection, and government support/expropriation are ignored.

Current regulatory barriers make it difficult to develop drugs aimed at large populations, let alone the small (and often poor) patient groups envisioned for these pediatric formulations. Unless 'fast-track' or special regulatory pathways are developed, most of these formulations will never pass the economic analysis within a pharmaceutical company. Perhaps using a transferable fast-track 'coupon' similar to that allowed with drugs intended for third-world infectious diseases would permit shifting some of the benefits of 'blockbuster' drugs to these pediatric dose forms.

Second, in economic analysis the benefit of pediatric formulations is further reduced by the extended liability. A company is at risk for at least 18 years for a drug given to an infant, and with current legal trends, it could be at risk for many more years. Some sort of liability protection would help balance the extra risk, which inhibits development.

Finally, most of these formulations will never be economically viable unless governments make a specific promise to support development and offset any expropriations by other governments. As can be seen in Thailand and other countries, it is in the self-interest of countries to take the IP for drugs that are "important to national health". Any pediatric drug is at risk. But due to the relatively small size of pediatric populations in the developed world, they alone are unlikely to support many pediatric formulations. If companies are expected to develop drugs based on the potential world-wide market, they must be protected from expropriation by the countries who have the biggest populations and most need.
6. Lynne M. Mofenson, M.D.
Pediatric, Adolescent and Maternal AIDS Branch
Center for Research for Mothers and Children
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health

Have reviewed the report and think it is very nice, and I have no comments to add. It is good to see that this group came to the same conclusions that the pediatric HIV drug group came to, and that the real need is for pediatric flexible solid dosage formulation.

7. H. William Kelly, Pharm.D.
Professor Emeritus of Pediatrics
Department of Pediatrics
Pediatrics/Pulmonary

I have read the document and have no specific issues with it.

8. Christopher-Paul Milne, D.V.M., M.P.H., J.D.
Associate Director
Tufts Center for the Study of Drug Development Tufts University

I have read the WHO report and have no comments. I would, however, draw the attention of the WHO group to a new book scheduled for publication in March on Pediatric Drug Development: Concepts and Applications edited by Andrew E. Mulberg, Steven A. Silber, and John N. van den Anker. Perhaps it will provide some them some assistance with their research questions.

9. Benedetto Vitiello, M.D.
Chief, Child & Adolescent Treatment & Preventive Intervention Research Branch
National Institute of Mental Health

I read the report and found it to be informative. The recommendations for further research seem reasonable to me.

Thank you for the opportunity to review this interesting and important document.

10. William Rodriguez, M.D., Ph.D.
Pediatric Science Director
Office of Pediatric Therapeutics
Office of the Commissioner
U.S. Food and Drug Administration

I read this very nice report and I only have a minor comment. Either as a footnote or comments there should be a mentioning of ongoing successful
collaboration amongst WHO, FDA, industry (private and generic sectors) manifested in the Pepfar experience in moving forward convenient and more readily accessible drugs for patients with HIV. This experience addresses amongst others many of the factors facilitating drug development for the population in developing countries (e.g. solid forms, weight band applications, educational approaches etc., etc).