The WHO Expert Subcommittee on Selection and Use of Essential Medicines for Children identified two terms of reference that needed further work and were the subject of this report. The first term of reference, e.g. “suitability criteria” is fairly adequately addressed. However, although the report outlines a list of ideal recommendations, it does not appear to adequately address “feasibility of manufacturing appropriate formulations…..” as articulated in the Second Term.

The assumption that the majority of priority medicines do not require precision dosing seems to sidestep the requirements for incremental dosing in the most vulnerable childhood population, e.g. infants and children less than 5 years. There is no clear evidence to support this assumption and some evidence against it. Precise dosing is particularly necessary for critical drugs that have a steep dose-response curve, e.g. narrow therapeutic index and for the youngest of patients.

Solid dosing formulations, as recommended, have clear advantages for packaging, shipping, storage, longevity, etc. However, the seeming assumption of the feasibility of manufacturing solid formulations which provide adequate incremental dosing for infants and toddlers along with acceptable palatability while employing existing solid formulation technology is probably too simplistic and unrealistic.

The proposal to disperse a solid formulation in breast milk raises a number of fundamental bioavailability issues and comes across as somewhat naïve.

Transcutaneous drug delivery technology presents major issues, particularly in infants and children <5 years. In addition to practical application and safety issues, it is difficult to incorporate satisfactory incremental dosing with this technology. Also, the body surface area relative to body mass changes dramatically across this age range adding an additional variable in drug delivery in this age group.

In summary, it seems some of the key feasibility challenges are glossed over or essentially ignored in arriving at some of the recommendations of the report.
2. **Julie A. Mennella, PhD**  
*Monell Chemical Senses Center*

I have read this informative and important 2008 report that reviews current knowledge on dosage forms of medicines for children as well as identifies research gaps in knowledge. I concur that developing and validating standards and methods for palatability testing in children is a priority. Also recommended is that the reporting of formulation information as it relates to palatability be included in future drug trials on children to improve validity and reliability of findings.

3. **Loyd V. Allen, Jr., Ph.D., RPh**  
*Editor-in-Chief  
International Journal of Pharmaceutical Compounding*

Many potential problems and variables have been identified and this is good. There are also some potential solutions proposed. However, there is still a lot that needs to be done.

I would suggest prioritizing first, then implementing and optimizing as more experience is gained. There are a LOT of potential solutions to this topic from the formulation standpoint that are feasible and will meet the potential difficulties that have been delineated. I would suggest moving forward in such a manner that many countries can be addressed first and those with special difficulties can follow…rather than talking about how we can do ALL of them at the same time.

4. **Emmett Clemente, Ph.D.**  
*Manchester Consulting Incorporated*

I believe the report addresses many of the current issues, and identifies specific problems that are necessary to solve to more appropriately treat children efficiently, and safely. I will try to narrow my comments to the stated aim of the report, which is to review existing evidence on appropriate pediatric formulations, and research needed to improve the development of preferred dosage forms. Additionally, these comments will be directed to off patented medications, and to children treated by office based pediatricians in areas of the world that are developed. This approach is not to avoid the real problems affecting proper treatment, and appropriate formulations for other parts of the world but an attempt to focus my comments. I do believe, however, that there will be scenarios that will be appropriate to both.

Information regarding the existing dosage forms that are used in children, by age, and percentage of use is available from market audit data (IMS, etc.), and demonstrates the preferred formulations. This data can be further analyzed to identify the products. This information can be compared to what appears in the literature, and will give a quick comparison. However, it will be specific for the territory in which the market audit data has been developed. Much of what a child prefers
can be obtained by conducting market focus studies with pediatricians, parents, and children. There are situations that an injection is the only option, and will be an approach that is “preferred” but not in the patient’s view.

Too much cannot be made of the taste profile, and mouth feel of the formulations. From my personal experience in developing products for thirty-five years, is the ideal formulation or young children is a low volume, good tasting, once a day solution. Tablets can be formulated with inert polymer coatings to mask bitterness. Again, it will be a plus to minimize the tablet size, and dosing frequency.

The meeting addressed diseases of high burden as a target to make the greatest impact in reducing childhood morbidity, and mortality. This may be the case, and the formulations’ issues that need to be solved overall, I would argue are very similar. The formulation constraints in pediatric medicine are not insurmountable, in my view, the technology is available. More important is the resolve to accomplish the goal, and an appreciation of the market dynamics necessary to achieve the result. There are several important considerations to provide our children with safe, and efficacious medications including the relevant age form, the technology to produce the product, the appropriate regulatory requirements, clinical, bioavailability studies, among others.

We often omit the commercial drivers in this equation, and I hasten to list, the importance of this variable. If a commercial organization believes that it can produce the product, and make a return on its investment the product will most likely be developed. We know that large pharmaceutical organizations are not interested in the pediatric market. It seems to me that if the resources, private funding, government commitment, alliances between dedicated pediatric companies, and “Big Pharma”, regulatory help, etc. are engaged, we have the greatest opportunity for success. As the technology to formulate the desired dosage form no matter for what market is here or can be developed, certainly for off patented drugs. New chemical entities have additional hurdles, and should be addressed.

My last comment concerns the scope of this effort. I would recommend a rather focused effort after defining the various aspects that the committee is addressing. There is nothing more stimulating than a project that sees the light of day.