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European Paediatric Formulation Initiative's (EuPFI) 2nd conference commentary—Formulating better medicines for children

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The adoption of Paediatric Regulation (EC) No. 1901/2006 and consequent demand for greater consideration for medicines for children has strengthened the focus on a need for development of age-appropriate formulations. A challenging subject, considering that there are still many open questions that the pharmaceutical, academic and the regulatory stakeholders have to deal with. European paediatric regulation had a significant, positive impact on achieving this goal whereby paediatric strategy has to be now part of every drug development programme, requiring paediatric data unless a waiver is appropriate. That said, paediatric medicine development is complex, resource and time intensive. The European Paediatric Formulation Initiative's (EuPFI) 2nd conference 'Formulating Better Medicines for Children' 2010, organised by APV (Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik or International Association for Pharmaceutical Technology) on 21st and 22nd September 2010 in Berlin, Germany, shed light on gaps in knowledge by providing an overview of the main challenges and issues related to development of paediatric formulations such as age-appropriateness of dosage forms, use of excipients, taste masking and taste assessment, administration devices, extemporaneous formulations, and new developments for the global market. It also aimed at providing a platform to exchange experiences and lessons learnt so far.

The conference was formally opened by joint conference chairs, Dr. Catherine Tuleu (The School of Pharmacy, University of London) and Prof. Jörg Breikreutz (University of Dusseldorf). Dr. Tuleu presented the aims and objectives of the EuPFI ongoing work stream activities (as found on www.eupfi.org). The plenary talks were targeted to gain a perspective on the regulatory and industrial considerations to address formulations needs of children including US and Developing World perspectives.

In addition to providing a better understanding of current paediatric research efforts, the conference focused on highlighting the challenges/barriers that impede progress, and explored bridges to overcome such barriers. Dr. Siri Wang (EMA) and Dr. Julie Williams (Pfizer) called attention to a range of formulation issues and challenges indentified/observed in Paediatric Investigation Plans (PIPs) submitted since the EU regulation came into force in January 2007. A considerable challenge in paediatric drug development lies in younger age group (neonates, infants). Dr. Williams and Dr. Wang presented various examples of quality questions raised by PDCO such as issues of taste, acceptability and palatability, excipients safety, appropriateness of parenteral formulations. A specific issue is having the age appropriate formulation sufficiently described even at an early stage. Dr. Wang highlighted the need for novel formulation and new research to overcome aforementioned issues, suggesting that some solid dosage forms (powders, granules, minitablets, (oro)dispersible dosage forms) may provide alternatives. For injectable formulations, appropriate drug concentrations and vial size should be considered to allow accurate and safe administration of a dose. For medicinal products supplied as single-use vials, consideration should be given to dose-appropriate

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single-dose packaging. Dr. Wang concluded that the basics are there but that what is needed in PIPs is proper background information with appropriate strategy information and justification. The main goal is to make paediatric drug development an integrated part of overall drug development program rather than just an 'add-on' even if considered early, so that the paediatric formulation and adult formulations are progressed together. This is a huge challenge due to the different patient expectations and considerations, but it needs to be reflected in PIPs.

Dr. Williams provided a risk/benefit approach which could be considered during paediatric formulation development and used to support the decision making process. She presented three theoretical case studies to which this risk benefit framework was applied and suggested that this could provide a helpful basis for discussion of what are most important considerations for formulation choices, recognising it is often necessary to balance many possibilities.

Two 'soap box' sessions gave individuals opportunity to share their work with the audience. During the first one, *Julia Hermann* (Freie Universität) presented results of a number of drugs with different physicochemical properties, each formulated as mini-matrix tablets. Employing matrix size, drug loading and preparation method as formulation tools, sustained release of 8–24 h could be achieved independent of the drug's solubility. This is a drug delivery technology offering flexible release patterns that may be easily and reliably dosed, as a range of individualised doses, to younger children.

Aranyos Attila (Alpha MOS) demonstrated the differences in taste using the electronic tongue Astree2, between an original famotidine orally disintegrating tablet and eight generic versions on the Japanese market. The instrument also allowed discrimination of products with considerable bitterness.

Smita Salunke (EuPFI) presented the outline for a pilot database compiling safety issues and toxicity aspects of excipients likely to be used in paediatric medicines. The database development will entail comprehensive manual retrieval, extraction and verification of the quality of information identified. She explained the methodology for systematic literature search, data collection, database development and utilization. This was followed by Dr. *Hussain Mulla* (University Hospitals of Leicester NHS Trust) presenting an assessment of quality and clinical performance of unlicensed liquid captopril formulations used in the treatment of children with heart failure. He highlighted that the unlicensed liquid formulations tested were similar in terms of physicochemical properties and thus pharmaceutically acceptable. Despite this they were not equivalent *in vivo and thus* healthcare professionals must not assume that any unlicensed formulations can always be used interchangeably in children. Prescribing bio-*in*equivalent formulations inter-changeably may contribute to unpredictable drug response and sub-optimal therapy, so formulation substitution must be done with care.

Klaus Wening (Heinrich-Heine-Universität Düsseldorf) presented the development of a dosage pen able to deliver individual solid doses of a new effervescent formulation. Such a dosage pen is suitable across a wide age range from children to geriatrics and could provide a new platform for paediatric formulations.

David Woods (Pharminfotech Consultancy and University of Otago) introduced the needs of developing countries with respect to paediatric formulations and administration which included (1) wider availability of paediatric formulations that are already commercially available elsewhere. This may be improved by liaising with regulatory authorities; (2) access to standardized formulas using simple ingredients for preparations that are not commercially available; (3) educational strategies to promote the use of rational and effective alternatives to extemporaneous formulations. He suggested some of the needs can be satisfied by replicating studies or encouraging parallel studies using available ingredients. There is also a need for a universal "generic" suspending base which could be used easily in countries that need it. Education and guidelines can be made available through E-learning tools.

The fast spaced soap box session was followed by a thematic session covering the five workstreams of EuPFI.

1. Industry-verified and extemporaneous preparations session chaired by Dr. John Hempenstall (GlaxoSmithKline)

Extemporaneous dispensing does not have a clear or legal definition within the European regulatory system for medicines, according to Prof. Anthony Nunn (Liverpool Children's NHS Trust/MCRN). It is usually understood as 'the manipulation by pharmacists of various drug and chemical ingredients using traditional compounding techniques to produce suitable medicines when no commercial form is available. However, it has also been used to describe the manipulation of authorised dosage forms such as splitting tablets or reconstitution of an authorised antibiotic powder mixture. It is possible that misunderstanding of terminology is contributing to apparent differences between industry and regulators when an extemporaneously prepared medicine is suggested during discussion of PIPs. Prof. Nunn suggested there should be a clear distinction between 'industry-verified [*extemporaneous*] preparations' and magistral formulations prepared by dispensing pharmacists to their own formula and method with very limited quality assurance. Manipulation of 'adult' dosage forms can be 'industry-verified' and included within a Marketing Authorisation (MA). Whilst all reasonable effort should be made to include an industry-manufactured age-appropriate dosage form in PIPs and MAs, use of an 'industry-verified preparation' or manipulation may enable the earlier conduct of clinical trials in children and may be acceptable for the final MA. This is acceptable only if formulation quality, safety and bioavailability can be assured by minimising variability in method of preparation included in the summary of product characteristics (SmPC) or patient information leaflet (PIL), as appropriate and recommending methods of quality assurance.

Doerine Postma (Laboratory of Netherland Pharmacists) explained that existing registered medicines in the Netherlands are often unsuitable for children because of inappropriate dosage forms or strength, or they contain excipients which are not acceptable for paediatric use. Dutch Pharmacists deal with this by following a three step process. Step 1 is to work with industry to try and bring appropriate products on the market. Step 2 is to advise doctors on acceptable alternative therapeutic products. Step 3 is to use pharmaceutical compounding either as standardised formulations or provide advice on how to develop alternative extemporaneous formulations. The Dutch formulary, Formularium der Nederlandse Apothekers (FNA, 2004) contains 200 standardised formulations which are all considered clinically appropriate. They are accompanied by comments on the formulation, a batch preparation record, a monograph, a comment on the clinical evidence, an instruction leaflet and it has a record in the national drug database (also known as "*G-Standard*") (Van Roon et al., 2005). When a new active compound is needed, Dutch pharmacists can follow one of the dosage form specific standard operating procedures (SOPs) provided by Royal Dutch Pharmacists Association (KNMP). These describe how to prepare basic dosage forms and which properties of the active compound should be taken into account with a risk assessment tool. Manipulation of a registered product is another way to make a suitable preparation for children, with Dutch handbooks having been developed to support safe (off-label) handling and administration of drugs for parenteral and oral dosing for patients with swallowing difficulties or through enteral feeding tubes. This information is derived mainly from SmPC's and product composition knowledge, with occupational health risks and the influence of enteral

feeding on bioavailability taken into account. It was suggested that it would be useful to combine such information at European level. If this happened, the first step would require translation of source material into a common language.

Following individual presentations, the speakers collectively participated as a panel to address questions from participants. One area of discussion was the possibility of an intermediate between industry verified preparation and adhoc preparations. This was exemplified through Dr. Mulla's former presentation. The speakers suggested there may be an alternative method of formulation appropriate for some drugs particularly where the therapeutic index is wide. Another important difference between industry and extemporaneous preparation is the source of the active pharmaceutical ingredient (API) and quality of raw material used. In an industry verified preparation, the API specification is approved for use from specific source from where it has been manufactured under good manufacturing practice (GMP) conditions while it is not necessarily the case for extemporaneous preparation from formulary. Risk benefit approach was further discussed as it is a common way regulators and industry may use in evaluating possibilities in product development. If industry can provide verified formula using locally accessible excipients/API this would improve patient access to a geographically diverse population. The other question raised was that while Industry verified preparations may address concerns for new drugs, how would older drugs be dealt with? Indeed there are many older established preparations that are neither licensed nor commercially available for children friendly formulations, where adhoc formulations have been produced and used successful clinically. In fact, official organisation like the British pharmacopoeia (BP) have recognised the issue and are producing performance monographs to provide the quality standards that should be achieved.

Another important point to be considered in the overall risk assessment is access to medicines for children. In that respect, UNICEF has put together a global virtual warehouse of products that identifies the location of products and dosage forms. This may help countries to source appropriate commercially available medicines and aid in decisions as to whether they should import a drug to their country or produce it locally by extemporaneous method. However, difficulties around importation or free movement of medicines between countries can complicate this process and it is also expensive. Price control is a major issue in importation of drugs.

2. Taste masking and taste testing session chaired by Dr. Richard Kendall (Merck Sharp and Dohme)

The inability of young children to swallow whole solid oral dosage forms, combined with parents' stated preference for liquids, leads many authorities in the field to conclude that the preferred oral drug formulations for infants and young children are liquids rather than solid dosage forms. However, the bitter taste of a paediatric formulation may be so overpowering for children that, on occasion, they refuse to ingest it, with potentially serious consequences. A better understanding of the scientific basis for distaste, and how to ameliorate it, is becoming increasingly recognised as a public health priority. This was a topic for discussion in the second focus session on taste masking and taste assessment. Dr. Julie Mennella (Monell Chemical Senses Center) reviewed the ontogeny of the taste system in humans, with an emphasis on the paediatric population. Recent advances in bitter taste research have led to the discovery of a new generation of molecules that may inhibit bitterness ("bitter blockers"), at the level of the bitter receptor cell or at one of the early transductive steps. Although a few commercial bitter blockers have now been identified, there is scant published literature on their efficacy in adults, and none in children. Dr. Mennella highlighted the need for basic research to determine how effective these blockers are and the substantial variation amongst individuals in terms of sensitivity to different bitter compounds, which is due in part to age and genetically determined receptor variation.

Dr. Anne Cram (Pfizer) reflected on the challenges of developing palatable oral paediatric formulations and the challenges of masking the taste of poorly palatable drug (Cram et al., 2009). These are encountered on a regular basis during development of oral paediatric medicines. Palatability is one of the most crucial factors influencing adherence to therapeutic regimens and consequently therapeutic outcomes. To overcome these issues, certain areas have been identified where further research may considerably simplify and accelerate the formulation development process. These include (1) development or optimisation of robust and reliable taste assessment or prediction techniques suitable for early drug product development. (2) Validation of adult taste panels, allowing transfer of results to the paediatric population. (3) Development of platform technologies with universal taste masking capabilities, e.g. encapsulation or complexation. (4) Development of 'flexible' dosage forms that take into account the taste preference of the paediatric patient, such as Children's Tylenol® with Flavour Creator or the Grünenthal SIP technology. She proposed a thorough review of available technologies and their potential benefits for children as the focus of another EuPFI reflection paper.

Discussions on taste masking and taste assessment revealed that despite being under researched, the texture of the medicine is also an important contributing factor to how children judge a medicine and whether or not they like it. There have been lots of efforts taken to avoid unpleasant bitter taste and increase the palatability for paediatric medicines, but what about the aftertaste? Dr. Mennella informed that there are various reasons for aftertaste sensation. It could be the consequence of bitter agents binding to bitter receptors that are also located in throat. Even when encapsulation is used to avoid unpleasant taste, aftertaste can occur depending on time it takes the formulation to dissolve.

3. Administration devices session chaired by Dr. Bénédicte Roger (Sanofi-aventis)

In the third session, challenges and recent developments in delivery devices were presented by Dr. Jenny Walsh (AstraZeneca) and novel approaches in pulmonary administration by Deborah Bickmann (Boehringer Ingelheim). Improving paediatric health includes the development of age-appropriate formulations that can be administered accurately to ensure the correct dose is provided repeatedly. Furthermore, acceptability and ease of use of a device with which the product will be administered, both from the patient and carer's perspectives, is required to facilitate dosing and patient compliance. When developing paediatric formulations, it is therefore important to consider the requirement for a delivery device at an early stage in the development process. The device must be technically capable of delivering the required dose in a "user friendly" way. The need for and type of delivery device will depend upon the formulation, age of patient and route of administration. Frequency and duration of dosing may also have an impact on device requirements.

Dr. Walsh reviewed delivery devices through example that are currently available for use via the oral, parenteral, ocular, and nasal routes of administration, and concluded that further research is required. Although many of these device innovations may offer tangible patient benefits such as improved accuracy and ease of dosing, there appear to be very few available on the market. This is likely to be due to high market entry barriers such as cost. The reimbursement by health insurance bodies may be especially critical if the newly developed products are more expensive than the

conventional products. Studies are required to assess device cost effectiveness, of which compliance should be a major decision factor.

Mrs Bickmann focused on inhalation devices for pulmonary administration. The treatment of acute and chronic airway diseases is a major issue, as they could be life-threatening; hence, from an ethical and economical point of view, there is a need to provide efficient, affordable inhalation products and corresponding devices with valuable performance. The design of paediatric inhalation products are challenged by different anatomical airway geometries compared to adults, understanding of the required breathing patterns and of crucial importance is acceptance by paediatric patient. Novel approaches for developing appropriately designed inhalation devices for pulmonary administration, taking into account the special needs of children, may be tested with *in vitro* and *in silico* models (Wachtel et al., 2010) initially, but clinical testing is needed to assess their efficiency.

Day two of the conference began with the presentation from Dr. Giacoia (Eunice Kennedy Shriver NICHD/NIH, USA), who presented the review of the paediatric formulation research and funding at NIH.

4. Age-appropriateness of formulations session chaired by Prof. Anthony Nunn (Liverpool Children's NHS Trust/MCRN)

Dr. Tuleu reported that children of different ages and abilities require different dosage forms to match their ability, for example to safely and confidently swallow tablets. Research is inconsistent at matching age and ability to swallow tablets but generally the smaller the tablet the easier it is for young children to cope and tablet inhalation is not listed amongst common ingestion of foreign bodies. There are learning strategies to help young children cope with swallowing tablets or capsules without or with aids (e.g. sprays and cups) but success is partial. Use of small particulates share many advantages of liquid and solid medicines and could be an economical platform technology for manufacturers. Several new patented advances have also been described to help administration (e.g. dose sipping technologies; Vismon® and Parvulet® technologies) but cost may be an obstacle to their widespread adoption. Proof of cost effectiveness versus therapeutic and compliance improvement needs to be further investigated. More studies are required to demonstrate the acceptability to children of various ages of different solid oral dose formulations. Chewing risks, palatability and socio-cultural acceptability of children of various ages should be investigated for further evidence of suitability of multiparticulates.

During the second talk Simon Bryson (University of Brighton) presented the initial outcomes of the Children's Medication Preferences (CHIMP) project. This work attempts to investigate if 'medication adherence is really a problem with children' and if 'formulation factors have an impact on adherence'? Using interviews with carers, children and clinicians initial results obtained challenge some of the current paradigms. This will provide information to assist in choosing the best formulation or administration strategy for different groups of children with long term illness. Mr Bryson highlighted factors influencing medication adherence. While differences exist in the methods of measuring adherence and non adherence and of the scientific rigor of the data generated, there is nonetheless a recognised problem of adherence to medication in paediatrics. Reported figures across a number of indications for non adherence range from 25% to 70% (Fiese and Everhart, 2006; Costello et al., 2004; Cohn, 2003; Gardiner and Dvorkin, 2006) but are on average higher than in adults. Various studies have demonstrated increased illness exacerbations, visits to the emergency department, morbidity, and mortality, in patients who are non compliant or non adherent to their treatment regimens (Cohn, 2003).

Questions from the audience reflected the continuing uncertainty about age and appropriate oral formulations and that there may be significant cultural differences that should be explored through further research.

In the second soap box session, Dr. *Gaia Colombo* (University of Parma) presented the development and characterisation of mesalazine multiparticulates for oral administration for delivery to the colon. The multiparticulates disperse easily in liquid facilitating administration to children. Lipidic microparticles prepared by spray congealing were gastroresistant and showed complete release in phosphate buffer in 4–5 h. Their wetability could be increased by spray drying agglomeration with mannitol/lecithin while preserving gastroresistance. This allows potential extemporaneous water dispersion and use in younger children that cannot swallow a capsule filled with the lipidic particles; it also potentially improves palatability hence acceptability.

Katharina Woertz (Heinrich-Heine-Universität Düsseldorf) discussed the use of taste sensing systems (electronic tongues) to evaluate the efficiency of different multicomponent mixtures of cyclodextrins in order to mask the taste of bitter tasting quinine hydrochloride. Two commercially available taste sensing systems were used: TS-5000Z (Insent, Japan) and the α-ASTREE2 (AlphaMOS, France). She illustrated that their capabilities differ but each could contribute to make these systems promising tools for rational formulation development for the paediatric population.

Dr. *Hans-Leonhard Ohrem* (Merck KGaA) illustrated that the release profile of orodispersible tablets (ODT) did not necessarily follow their fast disintegration. It can be explained by different surface areas and porosities of the excipients as well as retarding effects of polymers or swelling components. Hence, care should be taken in selecting ODT excipient system regarding tablet strength and dissolution profile in addition to disintegration time.

Roberta Richey (Alder Hey Children's NHS Foundation Trust) discussed the widespread manipulation of drugs for dose adaptation in paediatric secondary care. Using a systematic review and direct observations she identified current clinical practice of manipulation at the point of administration. This covered all inpatient clinical areas in a large regional paediatric hospital, a district general hospital and a large regional neonatal unit. Her ongoing research work came to the conclusion that there is neither good evidence nor clear guidance for practitioners to support this potentially unsafe practice.

Dr. *Begonia Delgado-Charro* (University of Bath) discussed transdermal iontophoresis as a delivery option for ranitidine, phenobarbital and midazolam in children. She showed that iontophoresis can deliver therapeutically meaningful fluxes of these drugs with acceptable patch areas. Iontophoresis controlled phenobarbital and midazolam input through intact and partially compromised skin, but further refinements of the technique would be required to control delivery of these two drugs through the highly compromised skin distinguishing premature babies.

Dr. *Sarah Branch* (MHRA) reflected on the evolution of PIPs into marketing authorisations. She also considered the impact of the European paediatric regulation requirement for the assessment of paediatric studies not submitted previously. Up to July 2010, nearly 700 PIPs had been submitted in Europe (72% for new medicines, 25% for existing products and only 3% for off-patent drugs intended for a new paediatric use). So far in the UK this had resulted in 6 licence applications from completed PIPs leading to new information on paediatric use or new formulations suitable for children. Up to July 2010, 2 of 26 procedures of published assessments for older studies led to inclusion of new paediatric populations for existing indications; 1 to a new indication; 2 products had safety data added while 7 had other new information or clarifications included. Paediatric study data had been added to 5 products while there were no changes recommended for the remainder. Initial progress may

appear slow but an increasing number of products is expected in the future specifically designed for the treatment of children.

Finally *Stephan Wiet* (McNeil Consumer Healthcare) presented the outcomes of personal interviews with over 100 children that suggested that softer chewy textures are preferred to harder traditional OTC solid forms. Parents and children (ages 6–11) evaluated drawings of 7 soft and chewy prototypes formulations and in addition children were provided placebos to taste. They were very appealing to both parents and children despite what each perceived as appropriate and acceptable could differ e.g. "candy-like" was rated lowest by parents and highest by children. To fulfil both the preferences of both parents and children, manufacturers must ensure that any new dosage form addresses the safety concerns through for example child-resistant packaging.

The soap session was followed by talk on 'Formulating medicines for developing countries' by Dr. Sue Hill (WHO headquarter, Switzerland). The major causes of mortality in children in the developing world are clearly defined (pneumonia, diarrhoea, malaria, neonatal pneumonia or sepsis) – as are effective treatments. However, many of the appropriate interventions remain unavailable or are in limited supply in resource-poor settings. In a review of progress towards Millennium Development Goal 4 (child survival) in 2006, there were no data available to describe coverage or availability of antibiotic treatment for pneumonia, and limited availability data on oral hydration therapy and antimalarials as three examples. As a preliminary study to document the availability of key children's medicines, a survey revealing poor availability of key essential medicines for children, was carried out in 14 countries in Central Africa. Dr. Hill informed that in order to improve access, WHO is working with partners to improve the availability and formulations for priority essential medicines for children. Medicines need to be available, affordable and acceptable to patients. Dr. Hill emphasized that substantial progress towards the millennium development goals will not occur without a major effort to improve availability and access to medicines for children.

5. Excipients session chaired by Carl Mroz (Colorcon/IPEC)

Mr Mroz introduced the excipient's focus session by stating that in a pharmaceutical application excipients are used to produce a suitable dosage form which enables the administration of a drug substance to a patient, permits convenience of use and promotes adherence to treatment. The excipient may have a very simple function such as a filler or diluent or may have a more sophisticated function within a drug delivery system, by controlling drug release. Although excipients are often described as inert, it is likely that many will have some effect on the body, and the mechanism by which they interact with an adult may be very different to that with a younger person who is still undergoing physiological development.

Piotr Kozarewicz (EMA), presented the current problematic situation in relation to the safety of preservatives through various examples (hydroxybenzoates, benzoic acid and its salts, sorbic acids and its salts). Use of substances such as solvents or co-solvents (e.g. propylene and butylene glycol) showing preserving properties needs justification in relation to their safety. The use of preservatives in medicines intended for newborns and young infants requires special consideration. Indeed the law restricts use of preservatives in food for young infants (Anton et al., 2004). Debate concerning the safety of preservative is still ongoing and before the final conclusions are reached more experimental data from safety studies is needed. The suggested approach is that preservative free formulations should be considered whenever possible. Instead of developing multidose liquid formulations requiring preservation, alternatives such as solid dosage forms (granulates, granules in sachets, bulk granules in bottle with measuring devices, individual 'dry' doses that can be converted to liquid immediately prior to use, etc.) should be investigated. When preservatives are required, the concentration should be at the minimum level and a thorough justification (in relation to a favourable benefit/risk balance) for the choice of the preservative should be provided.

Dr. Mulla discussed the exposure of preterm and term neonates to excipients. The results of a recent UK survey indicate that in some cases neonates are exposed to excipients such ethanol, propylene glycol at a level in excess to the acceptable daily intake for adults. Moreover the most common group of excipients are flavours and sweeteners which mean the majority of infants who cannot feed orally are exposed unnecessarily. It was advocated that there is an urgent need for clinical research into the safety of excipients at various stages of a child's development, investigating 'excipient kinetics' to allow the ability to define appropriate safe exposure levels. Current drug product labelling does not include sufficient quantitative and qualitative composition information to allow a health practitioner to make an informed decision on potential safety issues.

The meeting was a balanced combination of educational and social activities with many opportunities for networking with other interested parties from across the world (25 countries represented) supported by an interesting variety of presentations and posters covering a wide variety of subjects; something for everyone!

The message to take home was that the paediatric formulation strategy must be an integral part of an overall and global development plan that can accommodate regional and cultural differences. There are still many unanswered questions and for the time being a balance between a too lax and a too restrictive position on formulation issues is sought, keeping in mind the need to have high quality and clinically relevant pharmaceutical formulations for a vulnerable population with special needs. The patient is waiting and the preferred "dosage form" may not be achievable. Formulation development can be very challenging but it is important to apply sound scientific principles, consider overall risk-benefit and seek flexibility or compromise. In reality of not having sufficient evidence the "precautionary principle" should be applied.

The 3rd annual conference on 'Formulating better medicines for children' will be held in Strasbourg, France on 21st and 22nd September 2011 and encompass suggested topics such as biological, biopharmaceutical issues, innovative dosage forms, quality of ingredients in paediatric medicines, and discussion on the awaited *EMA Quality guideline on the pharmaceutical development of medicines for paediatric use* to enhance the programme.

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