European Paediatric Formulation Initiative

March 6, 2013

Warszawa, Poland

EuPFi Lead
Formulating Better Medicines for Children

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EuPFi Consortium

COMPANIES: AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, MSD, Novartis, Patheon, Roche, Sanofi
ASSOCIATIONS: ipec Europe, ACSM Association of Commercial Specialists Manufacturers
ACADEMIA: University of Liverpool, Heinrich Heine Universität Düsseldorf, UCL School of Pharmacy, University of Hertfordshire, University of Birmingham, GRIP
SPONSORS: Pfizer, Piramal Healthcare
OBSERVER: European Medicines Agency

EuPFi Objectives

- Sharing experiences and expertise through **interactive discussions** and feedback between industry, **academia, clinical and regulatory professionals.**
- Making the information (publications, reflection papers etc.) visible/available through website.
- To identify the issues and challenges associated with **development of paediatric formulation** in order to raise awareness and consider ways towards better medications and clinically relevant dosage forms for children
- Raising **awareness** through publications and regular conferences/workshops.
- Lobbying **to generate** funding to support future academic or industrial research worldwide.

EuPFi

Five workstreams

www.eupfi.org

- **Pharmaceutical Excipients** — STEP database: Database of safety and toxicity of excipients for paediatrics; 1 paper published; *1 in preparation*
- **Taste Masking and Testing** — 1 reflection paper published; 1 on taste masking technologies prior-to submission (Adv Drug Deliv Rev)
- **Administration Devices** — 1 reflection paper published
- **Extemporaneous Preparations and Dispensing** — 1 reflection paper published
- **Age Appropriateness of Formulation** — 1 reflection paper *in preparation*; *Paediatric biopharmaceutics*

Five workstreams

Pharmaceutical Excipients

Table 1. Excipients with elevated toxicological risk for subpopulations of paediatric and geriatric patients.

Excipient	Administration	Adverse reaction
Preterm and term neonates, infants < 6 months of age		
Benzyl alcohol	Oral, parenteral	Neurotoxicity, metabolic acidosis
Ethanol	Oral, parenteral	Neurotoxicity
Polyethylene glycol	Parenteral	Metabolic acidosis
Polysorbate 20 and 80	Parenteral	Liver and kidney failure
Propylene glycol	Oral, parenteral	Seizures, neurotoxicity, hyperosmolarity
Patients with reduced kidney function		
Aluminium salts	Oral, parenteral	Encephalopathy, microcytic anaemia, osteodystrophy
Polyethylene glycol	Parenteral	Metabolic acidosis
Propylene glycol	Oral, parenteral	Neurotoxicity, hyperosmolarity
Hypersensitive patients		
Azo dyes	Oral	Urticaria, bronchoconstriction, angioedema
Benzalkonium chloride	Oral, nasal, ocular	Bronchoconstriction
Chlorocresol	Parenteral	Anaphylactic reactions
Dextran	Parenteral	Anaphylactic reactions
Ivacreogolglycerol-ricinoleate	Parenteral	Anaphylactic reactions
Parabens	Oral, parenteral, ocular, topical	Allergies, contact dermatitis
Sorbic acid	Topical	Contact dermatitis (rarely)
Starches	Oral	Gluten-induced celiac disease
Sulfites, bisulfites	Oral, parenteral	Asthma attacks, rashes, abdominal upset
Wool wax	Topical	Contact dermatitis, urticaria

J. Breitkreutz, J. Boos, Exp. Opin. Drug Deliv. 4: 37-45 (2007)

Hyperosmolality in Small Infants Due to Propylene Glycol

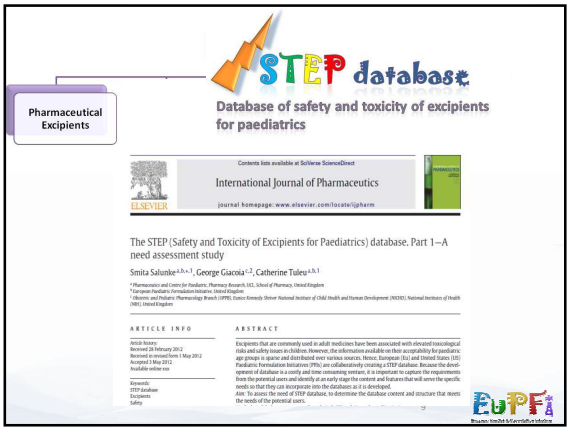
Glasgow et al., Pediatrics 72: 353 (1983)

Propylene Glycol: Increased Incidence of Seizures in Low Birth Weight Infants

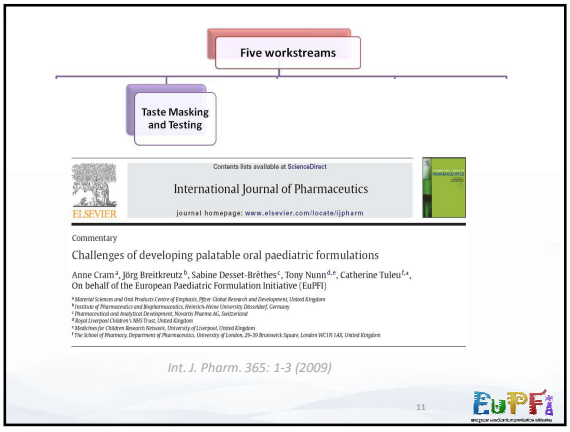
Getson et al., Pediatrics 79: 622 (1987)

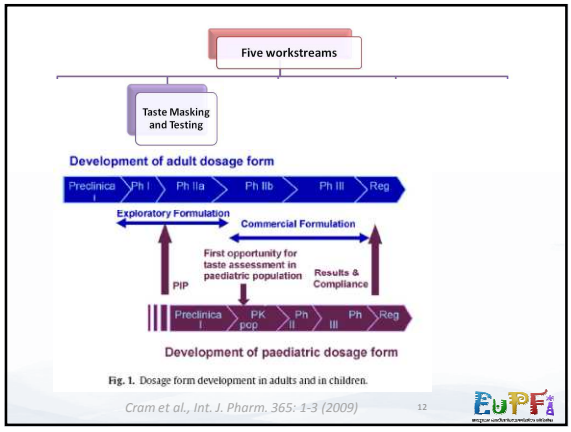
Propylene Glycol: The Safe Diluent that Continues to Cause Harm

Glover et al., Pharmacotherapy 16: 690 (1996)



GENERAL INFORMATION: Propylene Glycol
CAS No. 57-55-6
Synonyms: propanediol, 1,2-propanediol, Propylenglykol
Pharmacopoeial status: Ph Eur., BP
Regulatory status: GRAS
Functional classification: solvent, co-solvent, diluent, binder, plasticizer, antimicrobial agent
HUMAN FIELDS
Demographic (age, gender etc)
Administration/Exposure (E.g., Route, dose, concentration, duration etc)
Safety/Tolerability/Adverse effects findings by organ/system (e.g. GI, CVS, respiratory, etc.)
Pharmacokinetics/ADME
PK/PD relationship (dose- concentration relationship)
Acceptable daily intake
NON HUMAN FIELDS
Age. Juvenile/Adult) Species (e.g. rat, mouse, dog, non human primates.)
Administration/Exposure (e.g. Route, dose, concentration, duration etc)
Toxicity findings by organ/system (eg. Genotoxicity, hepatotoxicity etc,)
Toxicokinetics
Dose information (Eg., MTD, LD, NOEL, NOAEL)
In Vitro Data





Five workstreams

Taste Masking and Testing

- Development or optimisation of robust and reliable taste assessment or prediction techniques suitable for early drug product development, where limited toxicological information is available.
- Validation of adult taste panels, allowing transfer of results to the paediatric population.
- Development of platform technologies with universal taste masking capabilities, e.g. encapsulation or complexation. A thorough review of appropriate and available technologies would be beneficial. Taste enhancement approaches used in the food industry should not be overlooked when developing pharmaceutical products.
- 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.

In preparation

Cram et al., Int. J. Pharm. 365: 1-3 (2009)

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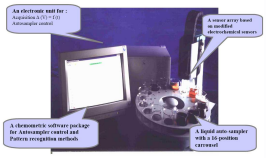
Five workstreams

Taste Masking and Testing

Ongoing project:
Etongue – User Group
Chair: Dr. M. Pein, Univ. Düsseldorf, Germany



Alpha-MOS

Insent

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Five workstreams

Administration Devices

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

Delivery devices for the administration of paediatric formulations: Overview of current practice, challenges and recent developments

Jennifer Walsh[a,*], Deborah Bickmann[b], Joerg Breitkreutz[c], Maryvonne Chariot-Goulet[d], on behalf of the European Paediatric Formulation Initiative (EuPFI)

Int. J. Pharm. 415: 221-231 (2011)

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Five workstreams

Administration Devices

Ongoing project:

International Questionnaire and Survey:
Handling and Appropriateness of Devices

Chair: Dr. Herbert Wachtel, Boehringer Ingelheim, Germany

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Five workstreams

Extemporaneous Preparations and Dispensing

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

Preparation of medicines for children – A hierarchy of classification

Terry B. Ernest[a,*,1], Jo Craig[a], Anthony Nunn[b], Smita Salunke[c], Catherine Tuleu[c], Joerg Breitkreutz[d], Rainer Alex[e], John Hempenstall[a]

ARTICLE INFO

ABSTRACT

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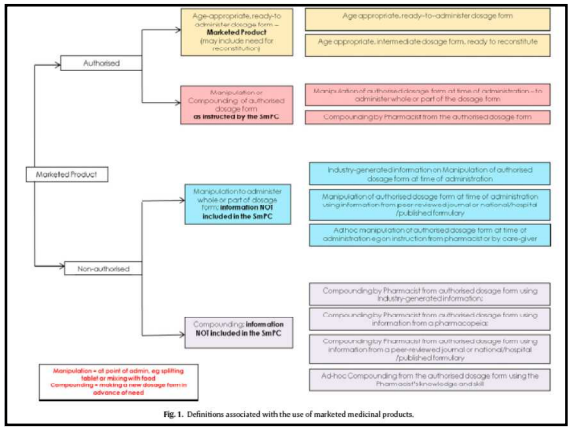
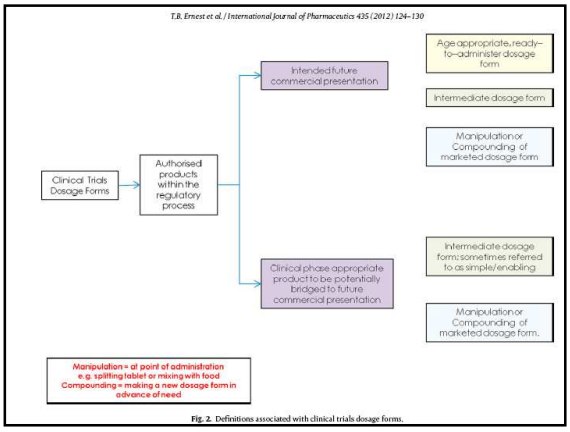
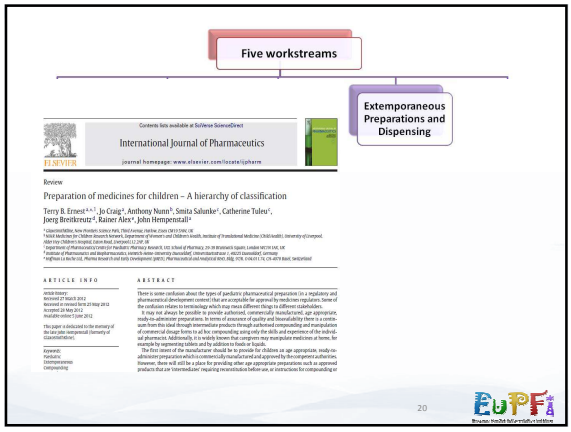
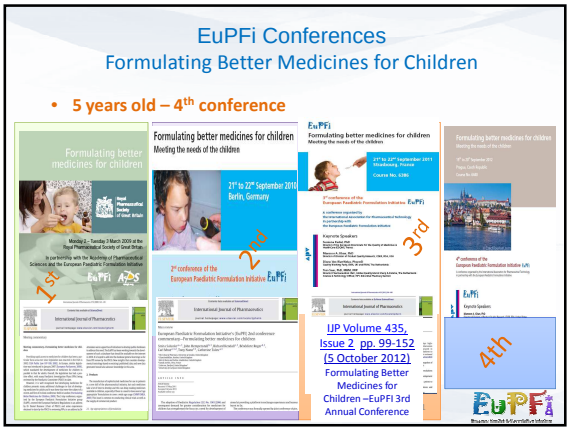
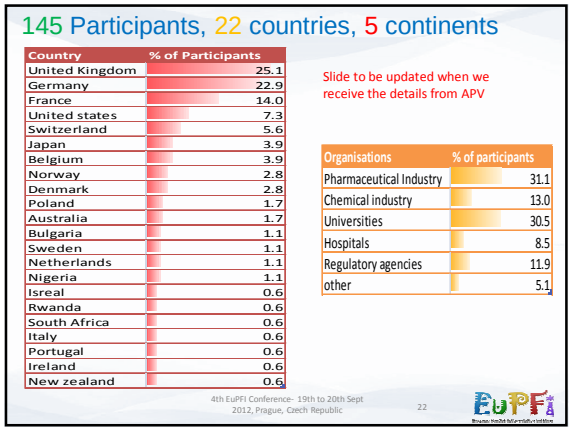


Fig. 1. Definitions associated with the use of marketed medicinal products.









Country	% of Participants
United Kingdom	25.1
Germany	22.9
France	14.0
United states	7.3
Switzerland	5.6
Japan	3.9
Belgium	3.9
Norway	2.8
Denmark	2.8
Poland	1.7
Australia	1.7
Bulgaria	1.1
Sweden	1.1
Netherlands	1.1
Nigeria	1.1
Isreal	0.6
Rwanda	0.6
South Africa	0.6
Italy	0.6
Portugal	0.6
Ireland	0.6
New zealand	0.6

Organisations	% of participants
Pharmaceutical Industry	31.1
Chemical industry	13.0
Universities	30.5
Hospitals	8.5
Regulatory agencies	11.9
other	5.1