


European Paediatric Formulation Initiative

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Warszawa, Poland





EuPFI Lead Formulating Better Medicines for Children

Dr Catherine Tuleu
Reader, Department of Pharmaceutics &
Director, Centre for Paediatric Pharmacy Research
UCL School of Pharmacy, UK
Secretary: Smita Salunke, cand. Ph.D.



Prof. Dr. Joerg Breitzkreutz
APV President
Head of Pharmacy Department
Institute of Pharmaceutics and Biopharmaceutics
Heinrich-Heine-University Düsseldorf, Germany

EuPFI Consortium

COMPANIES

AstraZeneca
Boehringer Ingelheim
gsk
GlaxoSmithKline
MSD
Merk Sharp & Dohme
Novartis
Patheon
Roche
Sanofi

ASSOCIATIONS

IPER
ACSM
Association of Commercial Speciality Manufacturers

ACADEMIA


UNIVERSITY OF LIVERPOOL
HEINRICH HEINE UNIVERSITÄT DÜSSELDORF
SCHOOL OF PHARMACY
UCL
UCL School of Pharmacy
UCL University of Hertfordshire
UNIVERSITY OF BIRMINGHAM
GRIP

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OBSERVER

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



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

www.eupfi.org

Five workstreams

Pharmaceutical Excipients

STEP database
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

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, hyponatremia
Patients with reduced kidney function		
Aluminum salts	Oral, parenteral	Encephalopathy, microcytic anaemia, osteodystrophy
Polyethylene glycol	Parenteral	Metabolic acidosis
Propylene glycol	Oral, parenteral	Neurotoxicity, hyponatremia
Hypersensitive patients		
Acid dyes	Oral	Urticaria, bronchoconstriction, angioedema
Benzalkonium chloride	Oral, nasal, ocular	Bronchoconstriction
Chlorobutol	Parenteral	Anaphylactic reactions
Desferal	Parenteral	Anaphylactic reactions
Macroglycerin-succinate	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. Breitzkreutz, 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)

GlaxoWellcome May 2000

IMPORTANT DRUG WARNING

RE: Potential safety concerns with the latest content of propylene glycol in AGENERASE[®]

BOXED WARNING (new statements in the box are underlined):

AGENERASE (amprolone) in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV RNA levels and CD4 cell counts in controlled studies of up to 24 weeks in duration. At present, there are no results from controlled trials evaluating long-term suppression of HIV RNA or disease progression with AGENERASE. Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or methotrexate.

CONTRAINDICATIONS AND WARNINGS:

AGENERASE Oral Solution should be used only when AGENERASE Cigars or other suitable inhibitor formulations are not therapeutic options.

Glaxo Wellcome Inc.
New York, NY 10017
New York, NY 10017
New York, NY 10017

U.S. Department of Health & Human Services
FDA U.S. Food and Drug Administration

Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products

Drugs

Home > Drugs > Drug Safety and Availability

Drug Safety and Availability

- Drug Alerts and Statements
- Importing Prescription Drugs
- Medication Guides
- Safe Use Initiative
- Drug Safety Communications
- Drug Shortages
- Postmarket Drug Safety
- Information for Patients and Providers
- Information for Drug Class
- Medication Errors
- FDA Drug Safety Newsletter
- Drug Safety Podcasts
- Drug Recalls

FDA Drug Safety Communication: Serious health problems seen in premature babies given Kaletra (lopinavir/ritonavir) oral solution

Safety Announcement
Additional Information for Patients
Additional Information for Healthcare Professionals
Data Summary

Safety Announcement
[3-8-2011] The U.S. Food and Drug Administration (FDA) is notifying healthcare professionals of serious health problems that have been reported in premature babies receiving Kaletra (lopinavir/ritonavir) oral solution. Kaletra oral solution contains the ingredients alcohol and propylene glycol. Premature babies may be at increased risk for health problems because they have a decreased ability to metabolize propylene glycol. This risk is greatest in babies who are born before 34 weeks of gestation or weigh less than 1,500 grams.

A safe and effective dose for babies less than 14 days of age (whether born premature or full term) has not been established.

Because the consequences of using Kaletra oral solution in babies immediately after birth can be severe or possibly fatal, the label is being revised to include a new warning. The use of Kaletra oral solution should be avoided in premature babies until 14 days after their due date, or in full-term babies younger than 14 days of age unless a healthcare professional believes that the benefit of using Kaletra oral solution to treat HIV infection immediately after birth outweighs the potential risks. In such cases, FDA strongly recommends monitoring for increases in serum somnolence, serum creatinine, and other signs of toxicity.

Kaletra oral solution is an antiviral medication used in combination with other antiretroviral drugs for the treatment of HIV-1 infection in pediatric patients 14 days of age (whether premature or full term) or older and in adults. Taking antiretroviral medications for HIV will not cure the infection, but can help children and adults with HIV-1 infection stay healthier for a longer period.

STEP database
Database of safety and toxicity of excipients for paediatrics

Contents lists available at ScienceDirect
International Journal of Pharmaceutics
journal homepage: www.elsevier.com/locate/ijpharm

The STEP (Safety and Toxicity of Excipients for Paediatrics) database. Part 1-A need assessment study

Smita Salunke^{a,b,*}, George Giacou^{a,c}, Catherine Tuleu^{a,b}

^aPharmaceutics and Center for Pediatric Pharmacy Research, UNC School of Pharmacy, United Kingdom
^bEuropean Pediatric Pharmaceutical Research, United Kingdom
^cPharmaceutics and Center for Pediatric Pharmacy Research, UNC School of Pharmacy, United Kingdom

ARTICLE INFO

ABSTRACT

Excipients that are commonly used in adult medicines have been associated with adverse neurological and safety issues in children. However, the information available on their compatibility for paediatric age groups is sparse and distributed over various sources. Hence, European Paediatric Pharmaceutical Research Initiative (EPRI) are collaboratively creating a STEP database. Because the development of databases is a costly and time-consuming venture, it is important to explore the requirements from the potential users and identify an early stage of the database that will serve the specific needs of the target user population. The purpose of this study is to explore the requirements for the development of a STEP database, to determine the database content and structure that meets the needs of the potential users.

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 (E.g., MTD, LD, NOEL, NOAEL)
In Vitro Data

Five workstreams

Taste Masking and Testing

Contents lists available at ScienceDirect
International Journal of Pharmaceutics
journal homepage: www.elsevier.com/locate/ijpharm

Commentary
Challenges of developing palatable oral paediatric formulations

Anne Cram^a, Jörg Breitzkreutz^b, Sabine Desmet-Beethes^c, Tony Nunn^{d,e}, Catherine Tuleu^{a,b}
On behalf of the European Paediatric Formulation Initiative (EuPFI)

^aEuropean Paediatric Pharmaceutical Research, United Kingdom
^bPharmaceutics and Center for Pediatric Pharmacy Research, UNC School of Pharmacy, United Kingdom
^cPharmaceutics and Center for Pediatric Pharmacy Research, UNC School of Pharmacy, United Kingdom
^dPharmaceutics and Center for Pediatric Pharmacy Research, UNC School of Pharmacy, United Kingdom
^eThe School of Pharmacy, Department of Pharmaceutics, University of London, 29-39 Brunswick Square, London WC1N 1AL, United Kingdom

Int. J. Pharm. 365: 1-3 (2009)

Five workstreams

Taste Masking and Testing

Development of adult dosage form

Predelivered Ph I Ph IIa Ph IIb Ph III Reg

Exploratory Formulation Commercial Formulation

First opportunity for taste assessment in paediatric population

Results & Compliance

Development of paediatric dosage form

Predelivered Ph I PK pop Ph II Ph III Ph Reg

Fig. 1. Dosage form development in adults and in children.

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

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 **in preparation** 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.

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

Insert

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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 Rickmann^b, Joerg Breitzkreutz^c, Maryonnie 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 ScienceDirect
International Journal of Pharmaceutics
journal homepage: www.elsevier.com/locate/ijpharm

Review
Preparation of medicines for children – A hierarchy of classification
Terry B. Ernst^{a,*}, Jo Craig^a, Anthony Nunn^b, Santa Salazar^c, Catherine Tuley^d, Joerg Breitzkreutz^e, John Himmelfarb^f

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

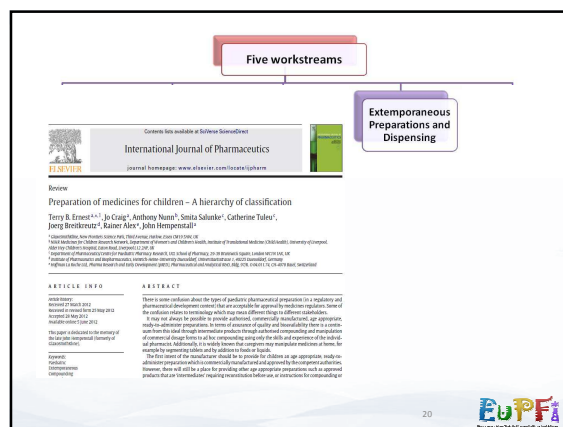
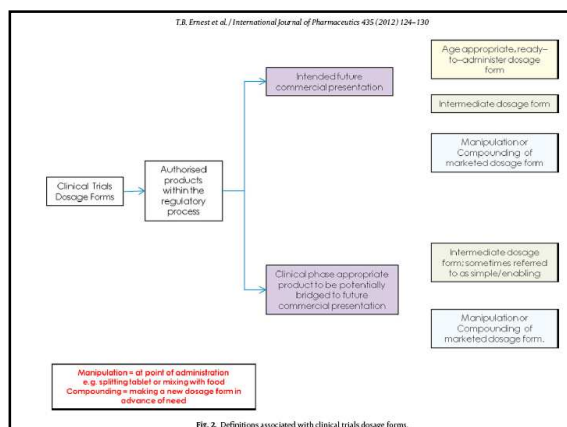
Authorized

Marketed Product

Non-authorized

Manipulation = all point of delivery, e.g. splitting, tablet or mixing with food
Compounding = making a new dosage form in advance of use

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EuPFI Conferences
Formulating Better Medicines for Children

- 5 years old – 4th conference

1st EuPFI Conference – 19th to 20th September 2011, Berlin, Germany
2nd EuPFI Conference – 19th to 20th September 2012, Berlin, Germany
3rd EuPFI Conference – 19th to 20th September 2013, Berlin, Germany
4th EuPFI Conference – 19th to 20th September 2014, Berlin, Germany

145 Participants, 22 countries, 5 continents

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
Israel	0.6
Rwanda	0.6
South Africa	0.6
Italy	0.6
Portugal	0.6
Ireland	0.6
New Zealand	0.6

Slide to be updated when we receive the details from APV

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

4th EuPFI Conference – 19th to 20th Sept 2012, Prague, Czech Republic

5th EuPFI conference

- 18th to 19th September 2013
- Barcelona
 - Hotel Porta Fira
- Preconference workshops (half 1st day)
 - Neonate/Pediatric pharmacology (GRIP)
 - How to write a PIP – quality section (EMA)
- 1.5 day conference. **NEW!** based on your suggestions:
 - Paediatric Biopharmaceutics
 - Patient and Public Involvement (PPI) in Formulation Research
 - Innovation show case
- Then every 2 years 2015, 2017 etc