Plenary 2:
SPaeDD-UK: Smart Paediatric Drug Development – UK
Accelerating paediatric formulation development
– an open innovation R&D project
Today’s aim

To share how UK Pharma and Academia are working collaboratively and innovatively to accelerate the development of new paediatric medicines
Content

• SPaeDD-UK – who we are
• Background to this project
• Co-funding of the project - Innovate UK
• The challenge
• The vision
• The project
• Exploitation plan
• Concluding remarks
Acknowledgements

This project brings together critical mass in the UK of expertise in paediatric formulation development from industrial partners, CMO/SMEs and academia as an R&D consortium to develop a novel suite of predictive analytical and in silico techniques and to develop methodologies to assess acceptability in children and evaluate age-appropriate dosage forms with the techniques/methodologies.
Acknowledgements

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- Peter Timmins (BMS)

**Academia**
- Hannah Batchelor (University of Birmingham)
- Punam Mistry (University of Birmingham)
- Nikoletta Fotaki (University of Bath)
- Giovanna Mencarelli (University of Bath)
- Catherine Tuleu (UCL)
- Abeer Mohamed Ahmed (UCL)
- Afzal Mohammed (Aston)
The Ten Commandments. Thou shalt...

1. License and market paediatric medicines
2. Account for age differences
3. Develop adequate paediatric medicines
4. Use safe excipients and levels
5. Design age appropriate formulations
6. Do more research in evidence based paediatrics
7. Optimise palatability/acceptability of formulations
8. Concentrate on paediatric biopharmaceutics issues
9. Improve unlicensed use of medicines
10. Help markets less well off
Innovate UK - R&D funding

Collaborative R&D Competition

**TSB and EPSRC** investing up to £6m in projects to accelerate the development of new ways of designing, improving and manufacturing complex high value formulated products

- Up to £5m for collaborative R&D projects.
- Up to £1m for feasibility projects.
- EPSRC will contribute up to £1m; where need for fundamental research is demonstrated.
- Typical total project size: CR&D £1m; feasibility £100k.
- Open 29th April; Phase I deadline 19th June.
- CR&D two-stage, Feasibility one-stage.
Innovate UK – what it is

• The UK’s innovation agency – a national body set up by government to stimulate business innovation – works at arm’s length from the Government
• Work across business and universities
• Responsible for investing £500M per year to drive and support innovation that will grow the UK economy
• Directly supporting 5000+ businesses across the UK

(formerly known as Technology Strategy Board – TSB)
Innovate UK – what it does

• Fund and support business led innovation
• Help businesses develop new ideas and technologies
• Support all types of business – pre-starts, start-ups, small and medium enterprises (SMEs) up to major corporations
• Work closely with UK universities
Paediatrics – why are we here?

• Paediatrics – why it is important
  – Unmet medical need
  – Recent (2007) regulatory requirements
  – Pharma has a paediatric portfolio to deliver
  – Pharma would like a “Gold standard” delivery platform for paediatrics
    • Regulatory expectation for industry to develop **age appropriate** dosage forms
    • Note - a single platform / dosage form that meets the needs of all age groups is a challenge!
Unmet medical need

Eight million reasons to do more

One statistic drives The Better Medicines for Children project towards success. Every year, an estimated 8.1 million children die before their fifth birthday, many because they do not have access to simple, affordable medicines.

• Developing countries are most acutely affected. Even basic, low-cost treatments such as zinc and oral rehydration salts for diarrhea are often unavailable. Yet these simple treatments could save millions of lives.

• When child specific medicines are not available, healthcare workers are obliged to adapt medicine intended for adults. Tablets are crushed into imprecise portions or dissolved into unpalatable drinks that are difficult to administer and potentially ineffectual or toxic.
Rewards, incentives and obligations

For unauthorised medicinal products

Marketing-authorisation applications for new medicinal products not authorised in the EU have to include the results of studies conducted in the paediatric population, in compliance with an agreed paediatric investigation plan (PIP), unless the European Medicines Agency has granted a deferral – i.e. the development is deferred until there are sufficient data to demonstrate the efficacy and safety of the product in adults. Waivers may also be granted when such paediatric development is not needed or not appropriate. Some medicines, such as generics, are exempt from these requirements.

Once authorisation is obtained in all Member States and study results are included in the product information, even when negative, the medicine is eligible for six months’ supplementary protection certificate (SPC) extension.

For orphan-designated medicinal products, the 10-year period of market exclusivity will be extended to 12 years.
## Paediatric Portfolio to Deliver

(Nasir Hussain, MHRA, APS 2015)

<table>
<thead>
<tr>
<th>Proposed dosage form</th>
<th>Therapeutic area</th>
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<tbody>
<tr>
<td>Capsule</td>
<td>Immunology</td>
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<td>Neurology</td>
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<tr>
<td></td>
<td>Oncology</td>
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<tr>
<td>Capsule - sprinkle</td>
<td>Allergology</td>
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<td>Granules</td>
<td>Neurology</td>
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<td>Pain</td>
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<td>Psychiatry</td>
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<td>Uro-nephrology</td>
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<td>Lozenge</td>
<td>Oto-rhino-laryngology</td>
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<td>Minitablets</td>
<td>Endocrinology</td>
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<td>ODT Minitab</td>
<td>Cardiovascular</td>
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<td>Haematology</td>
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<tr>
<td>Soluble tablet</td>
<td>Endocrinology</td>
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<td>Neurology</td>
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<tr>
<td>Solution</td>
<td>Anaesthesiology</td>
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<td>Cardiovascular</td>
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<td>Gastroenterology</td>
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<td>Psychiatry</td>
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<td>Uro-nephrology</td>
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<td>Suspension</td>
<td>Immunology</td>
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<td>Neurology</td>
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<td>Uro-nephrology</td>
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<td>Tablet</td>
<td>Cardiovascular</td>
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<td>Immunology</td>
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<td>Psychiatry</td>
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<td>Uro-nephrology</td>
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Number of Records
"Gold standard" delivery system

Bar chart showing the occurrences, as identified in the 2008 Strickley review, of 16 different types of prescription pediatric oral formulations

The past ...  ...the future
The challenge and the vision

• Regulations and financial incentives in place to mandate/encourage evaluation of medicines in children

• Provision of age-appropriate, safe and efficacious medicines to children is crucial yet challenging

• No industry standard available for paediatric product development

• Potential benefits to outsourcing of development and supply of paediatric medicinal products
Smart design and predictive science

- Ambition is to establish an industry standard framework and suite of tools to develop safe and efficacious paediatric dosage forms:
  - Taste evaluation
  - Acceptability testing
  - Prediction of human exposure in children
  - Technology platforms for paediatric medicines
SPaeDD-UK Workstreams

1. To develop novel in-vitro tools to predict the taste of paediatric medicines.

2. To develop novel analytical and in silico tools to predict the absorption of paediatric medicines.

3. To select regulatory acceptable UK-based encapsulation technologies and model drugs.

4. To determine patient needs in terms of acceptable formulation type.

5. To manufacture non-conventional formulation prototypes identified through evaluations from the previous stages.

6. To validate the proposed strategy and tools to demonstrate suitability for use in paediatric medicines development.
Workstream 1 - In vitro models for taste assessment

- Evaluating a number of in vitro models
  - E-tongue (GSK)
  - BATA “Rat lick” model (UCL)
  - Novel cell model (Aston)
  - Zebra fish (Pfizer)

- Lack of human dose response taste study data available to validate models
  - Generating additional human adult bitterness threshold data where gaps in data exist

Recent Pfizer taste study was $450K (without manufacture costs) and took 6-9 months
## WS1: Correlation of in-vitro testing with human taste data

<table>
<thead>
<tr>
<th>Compound</th>
<th>Human Test Data</th>
<th>BATA (Brief Access Taste Aversion)</th>
<th>eTongue</th>
<th>Cell Line</th>
<th>Zebrafish (exploratory)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>TBD</td>
<td>UCL</td>
<td>GSK</td>
<td>Aston</td>
<td>Pfizer</td>
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<tr>
<td>Sildenafil Citrate</td>
<td>UCL</td>
<td>UCL</td>
<td>GSK</td>
<td>Aston</td>
<td>Pfizer</td>
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<tr>
<td>Ranitidine Hydrochloride</td>
<td>GSK</td>
<td>UCL</td>
<td>GSK</td>
<td>Aston</td>
<td>Pfizer</td>
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<tr>
<td>Efavirenz</td>
<td>SRL</td>
<td>UCL</td>
<td>GSK</td>
<td>Aston</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Ibuprofen Na</td>
<td>Literature</td>
<td>UCL</td>
<td>GSK</td>
<td>Aston</td>
<td>Pfizer (Quinine/Caffeine/Paracetamol)</td>
</tr>
</tbody>
</table>
Work Stream 2 – paediatric biorelevant measurements and in silico predictions (Bath and BMS)

- Literature review to obtain paediatric PK data
- Physico-chemical/biopharm relevant solubility measurement
- In-silico PBPK model development
- Improved PK prediction

Process:
- Prototype formulations
  - Validate in vitro method
- Develop age-appropriate dissolution media/method

Additional notes:
- Literature review
- In-silico PBPK model development
- Improved PK prediction
Workstream 3 – Technologies for Taste Masking (AZ, Juniper, Pfizer)

• Data base compiled of different taste masking technologies

• Selected technologies to progress further and conduct further studies to evaluate:
  
  – Taste masked coated multiparticulates
  
  – Cyclodextrins and maltodextrins
  
  – Possibly other...
Workstream 3 – Technologies for Taste Masking

<table>
<thead>
<tr>
<th>Technology</th>
<th>API</th>
<th>Manufacture complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coated MP</td>
<td>Efavirenz, sildenafil and ranitidine (with placebo and uncoated control)</td>
<td>On-going</td>
</tr>
<tr>
<td>Cyclodextrins and Maltodextrins</td>
<td>Cross work stream APIs</td>
<td>On-going</td>
</tr>
</tbody>
</table>
Workstream 4 – Acceptability (Birmingham)

• Studies conducted to examine different methodologies for understanding “acceptability” in children.
  – 12 different hospitals
  – commercial products
  – various methodologies

• Assessment of acceptability of different multiparticulates formulations (size and coating)

The PDCO FWG recommend that acceptability, including palatability testing will be performed during clinical trials in target patients’ population.

Observation of facial expression and behaviours

Comparison of Methodologies for Judging Acceptability

“Did the medicine taste OK?”

“Did the medicine taste OK?”
Development of a Zebrafish Model for Bitter Taste Assessment

J. Bennett, A. Taylor, A. Coburn, A. Tyler, D. Stedman and A. Coupe
Pfizer Global R & D, Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK

Age related biorelevant dissolution testing for paediatric formulations

G. Mencarelli, J. Jones, J. Brown, P. Timmins, N. Fotaki
University of Bath, Dept of Pharmacy and Pharmacology, Claverton Down, Bath BA2 7AY
Bristol-Myers Squibb Pharmaceuticals Ltd, Uxbridge Business Park, Uxbridge, UB8 1DH
Evaluating the acceptability and mouthfeel of multiparticulates within a paediatric population

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1 School of Pharmacy, Institute of Clinical Sciences, University of Birmingham, Edgbaston, B15 2TT, UK
2 University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham, UK
3 Pfizer Global R & D, Ramsgate Rd, Sandwich, Kent CT13 9NJ.

Palatability and acceptability of multiparticulate formulations: Adults vs. children comparison

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3 Pfizer Global R & D, Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK
4 GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, CM19 5AW, UK
Innovate UK --- CDTs

Acceptability of multiparticulates: iUK-CDT collaboration

Obtain inner cores of varying size → Coating step → Adult leg (18-40 y/o)
Sensory evaluation: 500mg multiparticles, 5mL water (+150mL)
Children leg (6-12 y/o)

Data analysis → Acceptability of MPs?

CDT PhD student Felipe Lopez
UCL/GSK

Innovate UK
Birmingham / Pfizer

Pfizer
DRUG PRODUCT DESIGN
we design medicines
An evaluation of tools via patient-reported outcome measures to assess the acceptability of existing oral liquid medicines within a paediatric inpatient population.

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¹School of Pharmacy, Institute of Clinical Sciences, University of Birmingham, Edgbaston, Birmingham, UK.
²University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston Birmingham, UK
³University Hospitals Coventry and Warwickshire NHS Trust, University Hospital, Clifford Bridge Road, Coventry, CV2 2DX, UK
⁴CRN:West Midlands, NIHR Clinical Research Network (CRN), Institute of Research and Development, Birmingham Research Park, Vincent Drive, Birmingham, UK.
Workstream 6 Exploitation

- Acceptability assessment – method evaluation
- Bioavailability
- Taste masking
- Physicochemical characterisation

Framework for development
Conclusions

• Taste and taste evaluation
  – Is one of the most crucial factors influencing paediatric compliance and therapeutic outcomes
  – Should be understood early during drug development
  – Perception can be different between adults and children
  – Is difficult to assess in young children and need standardised methodology

• Taste masking
  – Is a major challenge, especially for liquid dosage forms
  – Ability to taste mask may influence dosage form design
  – Can significantly prolong product development timelines
    • Need for standard platform

“Drugs don’t work in patients who don’t take them.”
C. Everett Koop, MD US Paediatric Surgeon / Surgeon General
Conclusions

• Taste science
  – Has many exciting research opportunities - to help us develop even better paediatric medicines in the future!

• Collaborative R&D
  – Industry – academic collaborations really work!
    - include regulators for advice
    - draw on each others strengths/expertise
    - sharing of data
    - connect wider than the original project (CDT)
  – But be prepared for change
  – And be prepared for opportunistic funding

  “If you want to go fast, go alone, if you want to go far, go together!”
• Thank you and questions