Building Expertise in Pediatric Formulations

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ASCPT Annual Meeting
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Disclosure Statement

• I have no financial relationships to disclose relating to this presentation
The Real Life...

8 month old liver transplant recipient admitted for severe hepatic failure secondary to acute rejection

Tacrolimus blood level found to be extremely low

Lack of adherence by the mother was suspected along with parental neglect

Tacrolimus concentration in the compounded suspension prepared by the local pharmacy = 0.04 mg/mL = 1/10 of expected concentration
Nom de la préparation: TACROLIMUS 0.5 mg/ml (R) (active)

Format unitaire: 120ml

Ingrédients

1: TACROLIMUS 5 mg/caps.................................12 Caps
2: ORA-PLUS (vésicule).................................60 ml
3: SIROP SIMPLE.................................................60 ml
4: PRECAUTIONS.................................................1 app.
5: CONTROLE de la quantité de la poudre........1 form
6: MAGISTRALE CAPSULES.................................3 cate

Mode de préparation

1) Ouvrir et vider les capsules
2) Mouiller la poudre avec 1 ml d'ORACLIMUS
3) Ajouter le reste de 1 ml ORACLIMUS ainsi que le sirop simple par dilution géométrique pour obtenir un mélange homogène.
4) Bien mélanger.

Stability = 56 days
Parents find son's lifeless body after pharmacy switches sleep medication for toxic dose of another drug.
Problem Statement

• Many drugs administered to children are used off-label and are **not available** as **commercial pediatric formulation**
• Need for manipulation of dosage forms designed for adults by health care professionals and parents is associated with many challenges
  • Bad taste = impaired adherence
  • Limited stability data with no bioavailability data
  • Inaccurate dosing
  • Environmental safety from home compounding
  • Different manufacturing practices and quality control compared to pharmaceutical company standards
  • Lack of compounding standardization
  • No system in place to evaluate efficacy and safety of the compounded drugs
  • Lack of awareness of prescribers
Determinants of Effective and Safe Therapy

- Minimal/non-toxic excipients
- Palatable
- Minimal manipulation prior to use
- Flexible dosing
- Heat, humidity and light stable
- Easily produced
- Commercially viable
- Affordable

Availability of age-appropriate, innovative and high-quality pediatric formulations can spell the difference between successful treatment or therapeutic failure and safe therapy or adverse events.
Acceptable Oral Dosage Form(s) in Children?

2006: EMA: Reflection paper, Formulation of choice for the paediatric population

<table>
<thead>
<tr>
<th>Route</th>
<th>Dosage Form</th>
<th>Preterm newborn infants</th>
<th>Term newborn infants (0d-28d)</th>
<th>Infants and Toddlers (1m-2y)</th>
<th>Children (pre school) (2-5y)</th>
<th>Children (school) (6-11y)</th>
<th>Adolescents (12-16/18y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroral</td>
<td>Solution/Drops</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Emulsion/Suspension</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Effervescent DF*</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Powders/Multiparticulates</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Tablets</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Capsules</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Orodispersable DF</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Chewable tablets</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>
Formulations of Choice: a Moving Target

2008: WHO: Campaign “Make medicines child size”
• Recommendation of solid dosage forms in all age groups

2014: EMA: “Guidelines on pharmaceutical development of medicines for paediatric use”
• No age range recommendation for solid oral dosage forms any more
• Mini tablets and pellet approaches are considered more favourably
• Requirement of evidence for the suitability of solid dosage forms
Solid Oral Dosage Forms: Beyond the “Adult” Tablet

Dispersible tablet

Mini-tablet

Orodispersible film

Labelling of Enalapril from Neonates up to Adolescents
The GPFC Mandate

• To facilitate the development and market authorization of pediatric drug formulations by:
  • Promoting a research-based approach
  • Contributing to a favorable clinical and regulatory environment
  • Contributing to uncovering incentives
  • Promoting cost effective treatment for children

• To promote safety of medicines administered to children

Improving Access to Child-Friendly Medicines
The GPFC Strategy

Identify pediatric needs in Canada

Advocacy & awareness
Linking Stakeholders

Pediatric formulation availability?
Yes

Pharmaceutical partner(s) to develop ped. formulations and bring to market (Canada, US, EU ...)

No

Pharmaceutical partner to bring ped. form. to the Canadian market (and other countries)

• Services offered by GPFC
  – Clinical needs document to support the NDS
  – Guidance on using Third Party review strategy including Systematic Reviews
  – Accompany sponsors to Health Canada meetings to support the submission with clinical expertise
  – Expertise in design and conduct of pediatric studies

Understanding economics
Regulatory requirements

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– Clinical needs document to support the NDS
– Guidance on using Third Party review strategy including Systematic Reviews
– Accompany sponsors to Health Canada meetings to support the submission with clinical expertise
– Expertise in design and conduct of pediatric studies
Scoping the Needs for Oral Pediatric Formulations in Canada

• Which drugs are currently compounded for oral administration in Canadian children?
• Are they available in US and/or EU as commercial pediatric formulations?
• Which ones should we prioritize first?
Drugs Frequently Compounded in a Canadian Pediatric Tertiary Hospital

• 60 drugs were identified
• 3 most frequent categories of drugs using AHFS Pharmacologic-Therapeutic classification:
  • Cardiovascular: 30 %
  • Central nervous system: 18 %
  • Anti-infectious: 10 %
• 98% are off-patent drugs
• On the Canadian market for a median of 35 years (14 – 65 years)
• Canadian pediatric indication for 23 drugs (38%)
## Availability of Commercial Pediatric Oral Formulations in US and/or EU

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
<th>N=60, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>▪ Liquid form with known safe ingredients</td>
<td>15 (25)</td>
</tr>
</tbody>
</table>
| 2        | ▪ Liquid form containing one or more ingredients with potential safety concerns in children (N= 14)  
▪ Non-liquid oral form requiring manipulation by the parent before administration (e.g., powder or granules for oral suspension) (N=3)  
▪ Chewable tablets (N=1)                                                      | 18 (30)    |
| 3        | ▪ No commercialized pediatric oral formulation in US or EU                   | 27 (45)    |
Why Do We Have to Compound Medicines when Suitable Pediatric Formulations Exist?

<table>
<thead>
<tr>
<th>Pediatric formulation availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
</tr>
<tr>
<td>Caffeine</td>
</tr>
<tr>
<td>Enalapril</td>
</tr>
</tbody>
</table>
Still Splitting Tablets to Treat Leukemia...

- In Canada, 6-mercaptopurine:
  - Approved for the treatment of ALL
  - Available only as 50 mg tablet resulting in:
    - Tablet splitting
    - Compounded liquid oral formulation
  - Consequences of underdosing or overdosing can be catastrophic
  - Environmental toxicity related to compounding
  - Prolonged treatment

Approved and marketed in EU (2012) and US (2014)
Pan-Canadian Survey: Prioritization of Needs

• Thirteen centers among 16 contacted completed the telephone survey between April and June 2017 (81.3%)

• When sites were asked to list their 10 compounded medicines most in need of commercialized pediatric formulations:

A total of 51 drugs were identified
Drugs Most in Need of Commercialized Oral Pediatric Formulations in Canada

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Number of hospitals that ranked drug as:</th>
<th>Availability of pediatric oral formulations outside of Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Most in need of a pediatric formulation, n (%) N=13</td>
<td>Most frequently compounded, n (%) N=13</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>8 (62)</td>
<td>10 (77)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>8 (62)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>8 (62)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Clonidine</td>
<td>7 (54)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>6 (46)</td>
<td>6 (46)</td>
</tr>
<tr>
<td>PPI¹</td>
<td>6 (46)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>ACE inhibitors³</td>
<td>4 (31)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>4 (31)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>4 (31)</td>
<td>10 (77)</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>4 (31)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>4 (31)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>4 (31)</td>
<td>4 (31)</td>
</tr>
</tbody>
</table>

¹Proton pump inhibitors; ²for omeprazole and esomeprazole in the US and for esomeprazole in Europe; ³Angiotensin converting enzyme inhibitors (captopril, enalapril); ⁴contains propylene glycol and sorbitol; ⁵contains sorbitol
<table>
<thead>
<tr>
<th>Year</th>
<th>Region</th>
<th>Approval Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>US</td>
<td>Tablets approved for adjunctive therapy for POS in adults</td>
</tr>
<tr>
<td>2000</td>
<td>EU</td>
<td>Tablets approved for adjunctive therapy for POS in adults</td>
</tr>
<tr>
<td>2002</td>
<td>EU</td>
<td>Oral Solution approved for adjunctive therapy for POS in adults</td>
</tr>
<tr>
<td>2003</td>
<td>Canada</td>
<td>Tablets approved for adjunctive therapy for POS in adults</td>
</tr>
<tr>
<td>2003</td>
<td>US</td>
<td>Oral Solution approved for adjunctive therapy for POS in adults</td>
</tr>
<tr>
<td>2005</td>
<td>US &amp; EU</td>
<td>Tablets/Solution approved for adjunctive therapy for POS in adults and children ≥ 4 yrs</td>
</tr>
<tr>
<td>2006</td>
<td>US &amp; EU</td>
<td>Tablets/Solution approved for adjunctive therapy for JME in adults and children ≥ 12 yrs</td>
</tr>
<tr>
<td>2007</td>
<td>US</td>
<td>Tablets/Solution approved for adjunctive therapy for PGTC in adults and children ≥ 12 yrs</td>
</tr>
<tr>
<td>2007</td>
<td>EU</td>
<td>Tablets/Solution approved for adjunctive therapy for PGTC in adults and children ≥ 12 yrs</td>
</tr>
<tr>
<td>2009</td>
<td>EU</td>
<td>Tablets/Solution approved for adjunctive therapy for POS in adults and children ≥ 1 mth</td>
</tr>
<tr>
<td>2011</td>
<td>US</td>
<td>Tablets/Solution approved for adjunctive therapy for POS in adults and children ≥ 1 mth</td>
</tr>
<tr>
<td>2017</td>
<td>Canada</td>
<td>NO PEDIATRIC INDICATION AND NO PEDIATRIC FORMULATION EXIST TODAY</td>
</tr>
</tbody>
</table>

**Acronyms:**
- **POS** = Partial onset seizure
- **JME** = Juvenile myoclonic epilepsy
- **PGTC** = Primarily generalized tonic-clonic seizure
Why Aren’t Pediatric Formulations Being Made Available in Canada?

• Regulatory pathway perceived as unclear or complex
• Market size too small
• Incentives are few
• Seeking reimbursement viewed as challenging
## Regulatory Incentives for Pediatric Medicines

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Incentives for Patented Products</th>
<th>Incentives for Off-Patent Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>+ 6 months added to 8-year period of data protection</td>
<td>None</td>
</tr>
</tbody>
</table>
| US             | + 6 months of market protection to patents and/or exclusivity  
|                | 505 (b)(2) : 3-5 years exclusivity  
|                | Rare pediatric disease priority review voucher possible to keep or to sell | 505 (b)(2):3-5 years exclusivity |
| EU             | + 6 months to Supplementary Protection Certificate (SPC) if compliance with agreed PIP  
|                | + 1 year market protection if clinical studies required and MA granted  
|                | Orphan- +2 years of market exclusivity if PIP is completed for orphan indication = 10 + 2 | PUMA – 10 year marketing exclusivity |
Approved PUMA Drugs over 10 Years

- Midazolam oral solution (Therakind / Viforpharm)
- Glycopyrronium bromide oral solution (Provecia)
- Propranolol oral solution (Pierre Fabre)
Pediatric Formulation: Pricing Considerations

Higher per-patient costs

Costs to Develop and Manufacture a Pediatric Formulation

• Costs are affected by:
  • Complexity of the formulation
  • Extent of pre-clinical and clinical testing required by the regulatory authorities
  • Costs of regulatory filing
  • Size of the market
  • Length of market exclusivity, if any -> predominance of « off-patent » drug use in the pediatric setting

Cost of development: $500,000-15 million
Time: 2-6 years (2 yrs R&D)

Current Pathway Leading to Drug Access in Canada

Industry

Health Canada

Pan Canadian Pharmaceutical Alliance (pCPA)

Priority based on business

Regulator (Efficacy & safety)

HTA (Assess value)

Value negotiator

CDR (CADTH)

pCODR (CADTH)

Quebec (INESSS)
Hemangiol in Canada

Published literature and input from Canadian clinical experts indicated that the current preferred first-line treatment for patients with IH in Canada is compounded propranolol tablets...

Although the HC review indicates there is a need for a safe, effective, consistent, and high quality treatment for IHs requiring therapy, CDR notes there is a substantial incremental cost for the submitted propranolol oral solution.

Hemangiol: $273.70 per 120 mL bottle, 450 mg
Oral propranolol tablets: $1.2084, 450 mg
Excipient and compounding fees: $9.71 to ~$30 per 450 mg
What About Trying a New Model for Pediatric Formulations for Off-Patent Drugs?

STREAMLINING and HARMONIZATION of the regulatory requirements ACROSS jurisdictions (FDA, EMA, HC, Japan, Australia, etc…)

PATIENT-CENTRIC needs

Better global access of quality medicines for children

INCENTIVES

ONE MARKET AUTHORIZATION APPLICATION

“One stop shop”

Accelerated process
Commercially viable
Pricing -> Affordable
Conclusion

• Children deserve high quality pediatric formulations meeting their needs to ensure safe and effective pharmacotherapy

• For new patented medicines, there are regulatory requirements as well as incentives in the US and EU to ensure the development of pediatric formulations

• For off-patent medicines, there is still a huge unmet need for the development and access of suitable dosage forms for children despite the availability of incentives -> need to define a new model
Working together we can make a difference.....

• GPFC is currently supporting a pharma company with two medicines, one of which is using a NDS relying on Third Party Review process
• We are looking for more partners
• We are speaking to major stakeholders
• We are willing to collaborate with international organizations
• Pharmaceutical companies that partner with us have a tremendous opportunity to be leaders

We leave you with a video:  
https://www.youtube.com/watch?v=4kDxlhabb7I&feature=youtu.be
Dr. Catherine Litalien, Executive Director, GPFC
514-773-8212
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Andrea Gilpin, General Manager, GPFC
514-465-2114
agilpin.cfpg@gmail.com

merci
BACK-UP SLIDES
How Can We Move Forward with these Prioritized Drugs?

**From a regulatory perspective**

<table>
<thead>
<tr>
<th>Ped formulation available</th>
<th>Ped indication in Canada and US ± EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine, enalapril, lisinopril, 6-mercaptopurine, PPIs</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam, sildenafil</td>
<td>NO ped indication in Canada but ped indication in US ± EU</td>
</tr>
</tbody>
</table>

**“Suboptimal” Ped formulation or NO Ped formulation available**

<table>
<thead>
<tr>
<th>Dexamethasone, tacrolimus, topiramate</th>
<th>Ped indication in Canada and US ± EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone, clonidine, hydrochlorothiazide, hydroxyurea</td>
<td>NO Ped indication in Canada</td>
</tr>
</tbody>
</table>
Toward Better-Quality Compounded Drugs — An Update from the FDA

Janet Woodcock, M.D., and Julie Dohm, J.D., Ph.D.

Table 2. Examples of Adverse Events Associated with Drugs Prepared by Compounding Facilities over the Past 5 Years.

<table>
<thead>
<tr>
<th>Year</th>
<th>State</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>Indiana</td>
<td>Several neonates experienced oversedation after receiving superpotent compounded midazolam.</td>
</tr>
<tr>
<td>2016</td>
<td>Indiana</td>
<td>Three infants had serious adverse events after receiving compounded morphine sulfate that was nearly 2500% as potent as it should have been.</td>
</tr>
</tbody>
</table>
U.S. Project Going Global

Standardize 4 Safety

https://www.ashp.org/Pharmacy-Practice/Standardize-4-Safety-Initiative
The birth of PaedForm

A pan-European Paediatric Formulary

Prof Dr Jörg Breitkreutz
Heinrich-Heine-Universität, Düsseldorf

Dr Dirk Leutner
EDQM, Council of Europe
## Public reimbursement status (WW)

<table>
<thead>
<tr>
<th>Country</th>
<th>Public reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>Individual reimbursement - No general reimbursement</td>
</tr>
<tr>
<td>Belgium</td>
<td>YES</td>
</tr>
<tr>
<td>CZ</td>
<td>YES</td>
</tr>
<tr>
<td>Canada</td>
<td>Ongoing process</td>
</tr>
<tr>
<td>Denmark</td>
<td>Individual reimbursement - No general reimbursement</td>
</tr>
<tr>
<td>Finland</td>
<td>YES</td>
</tr>
<tr>
<td>France</td>
<td>YES</td>
</tr>
<tr>
<td>Germany</td>
<td>YES</td>
</tr>
<tr>
<td>Italy</td>
<td>YES</td>
</tr>
<tr>
<td>Japan</td>
<td>YES</td>
</tr>
<tr>
<td>Korea</td>
<td>Ongoing process</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>YES</td>
</tr>
<tr>
<td>Netherlands</td>
<td>YES</td>
</tr>
<tr>
<td>Norway</td>
<td>Individual reimbursement - No general reimbursement</td>
</tr>
<tr>
<td>Romania</td>
<td>Ongoing process</td>
</tr>
<tr>
<td>Spain</td>
<td>YES</td>
</tr>
<tr>
<td>Sweden</td>
<td>YES</td>
</tr>
<tr>
<td>Switzerland</td>
<td>YES</td>
</tr>
<tr>
<td>USA</td>
<td>No general reimbursement system, but covered by Medicaid</td>
</tr>
<tr>
<td>Croatia</td>
<td>YES</td>
</tr>
<tr>
<td>Greece</td>
<td>YES</td>
</tr>
<tr>
<td>Portugal</td>
<td>YES</td>
</tr>
<tr>
<td>Slovakia</td>
<td>YES</td>
</tr>
<tr>
<td>Slovenia</td>
<td>YES</td>
</tr>
</tbody>
</table>
Payment of drug costs

% of Canadian spending on prescribed drugs, 2014

- Public plans: 42.6%
- Private insurance: 35.2%
- Out-of-pocket: 22.2%

Source: Canadian Institute for Health Information (CIHI), Prescribed Drug Spending in Canada, 2016: A Focus on Public Drug Programs. 2015