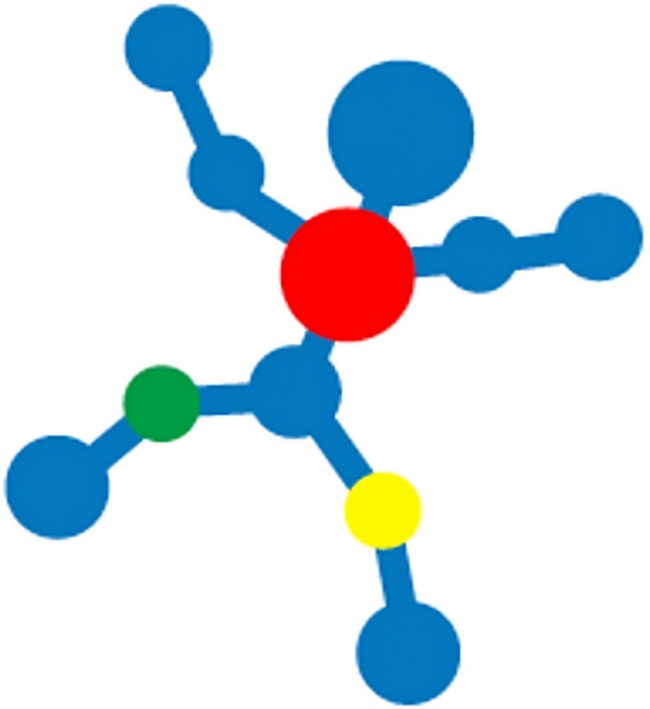
O Canada, We Stand Cautious and Slow-Moving for Thee



Dr. Raphaël Kraus, Assistant Medical Director

On behalf of the Goodman pediatric Formulations Centre (GPFC)

15th Conference of the EuPFI

Glasgow, Scotland, UK

September 20, 2023


ELIXIR
SULFANILAMIDE
ELIXIR
SULFANILAMIDE

Editorial comment: Therapeutic orphans

BY AN ODD and unfortunate twist of fate, infants and children are becoming "therapeutic or pharmaceutical orphans."[1] Since 1962 they have been denied the use of many new drugs. The Drug Laws of 1962 had their inception following a pediatric tragedy—the thalidomide catastrophe. The laws of 1938 followed another which resulted from the use of a pediatric dosage form, "elixir" of sulfanilamide. By "legal" definition, drugs introduced since 1962 must be safe and efficacious, but only a small number of these have been studied in the pediatric age group. Certainly, there are some drugs

Although the laws were designed to ensure the efficacy and safety of drugs, *the age group responsible for their passage* is now often deprived of the use of the medications. Testing of these drugs can not always be in controlled situations, but is sometimes in the situation of use—by ordeal and often against advice. Inevitably this "unlawful" procedure will be associated with some adverse reactions, including toxic reactions, side effects, and idiosyncrasy. These reactions are common to all drugs. History has also taught that drugs previously considered harmless may be associated with temporary and per-

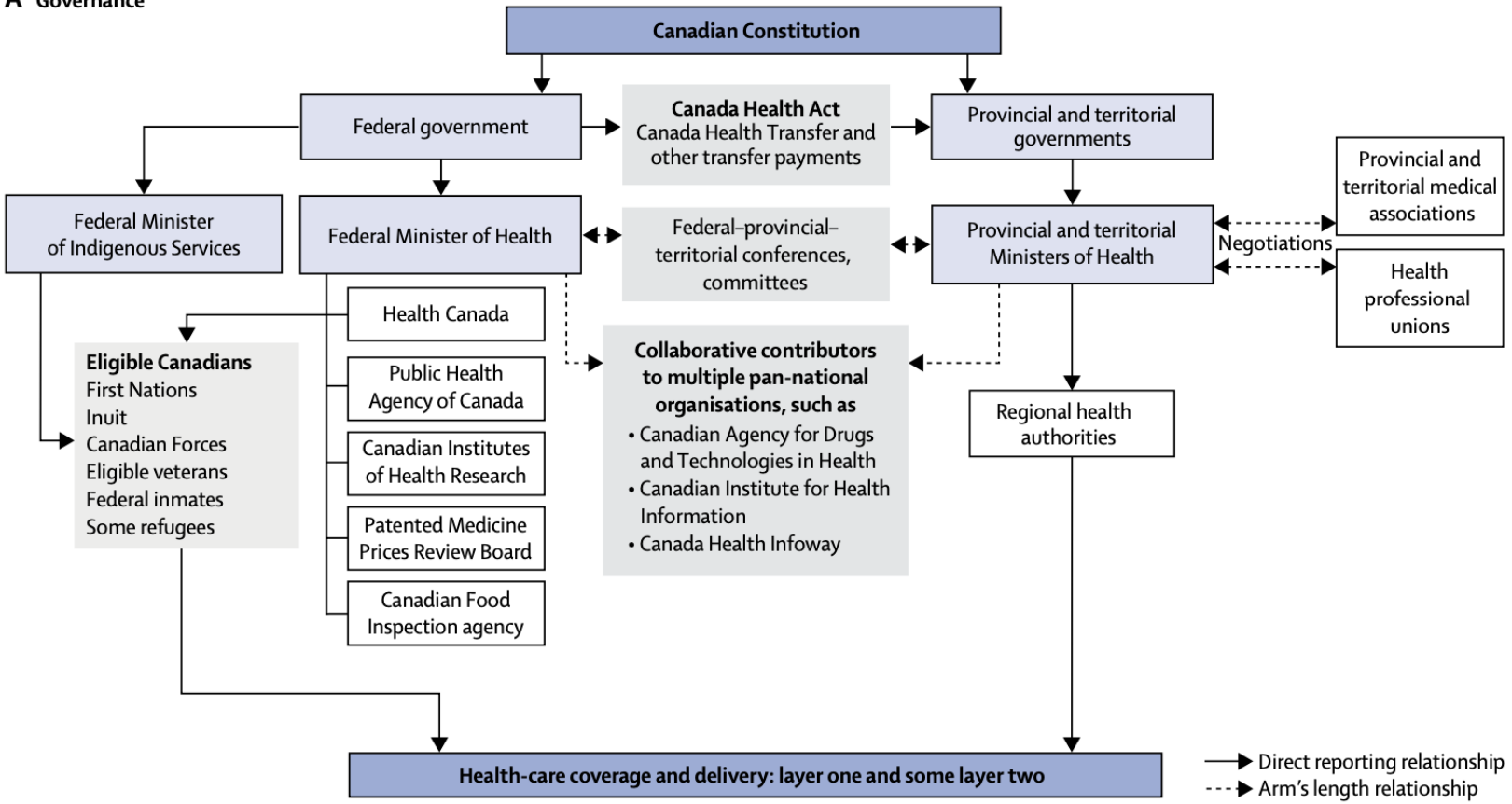
When America Sneezes…

- ~50-80% prescribed off label
- ~50% pediatric-specific information
- ~30% pediatric-specific indications

- x2 new pediatric drugs approved
- US: ~60% more new pediatric indications
- EU: ~30% more new pediatric indications

Raja 2020

A Governance



B Coverage

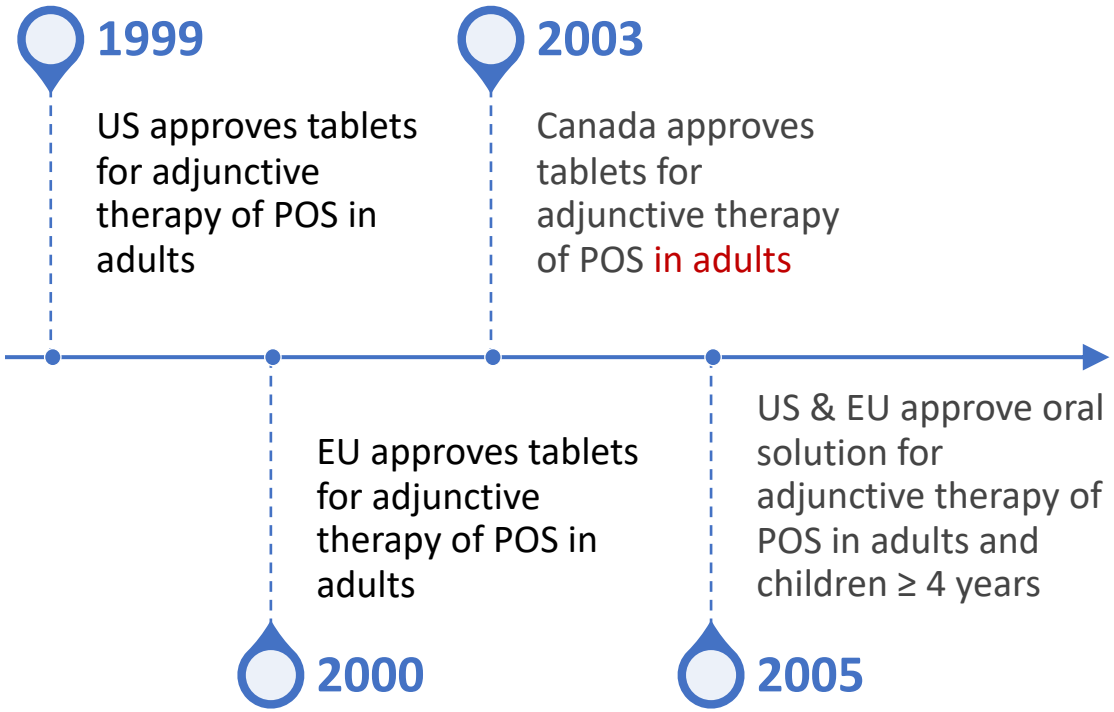
	Services	Funding	Administration	Delivery
Layer one Public services (Medicare): all public funding	Hospitals Physicians Diagnostics	Public taxation	Universal single-payer systems Private self-regulating professions	Private professional for-profit and not-for-profit facilities, and public arm's length facilities
Layer two Mixed services: combination of public and private funding	Prescription drugs Home care Long-term care Mental health care	Public taxation Private insurance Out-of-pocket payments	Public coverage is targeted Public regulation of private services	Private professional for-profit and not-for-profit facilities, and public arm's length facilities
Layer three Private services: almost all private funding	Dental care Vision care Complementary medicine Outpatient physiotherapy	Primarily private insurance, out-of-pocket payments, with some public taxation	Private ownership Private professions Limited public regulation	Private professional for-profit facilities

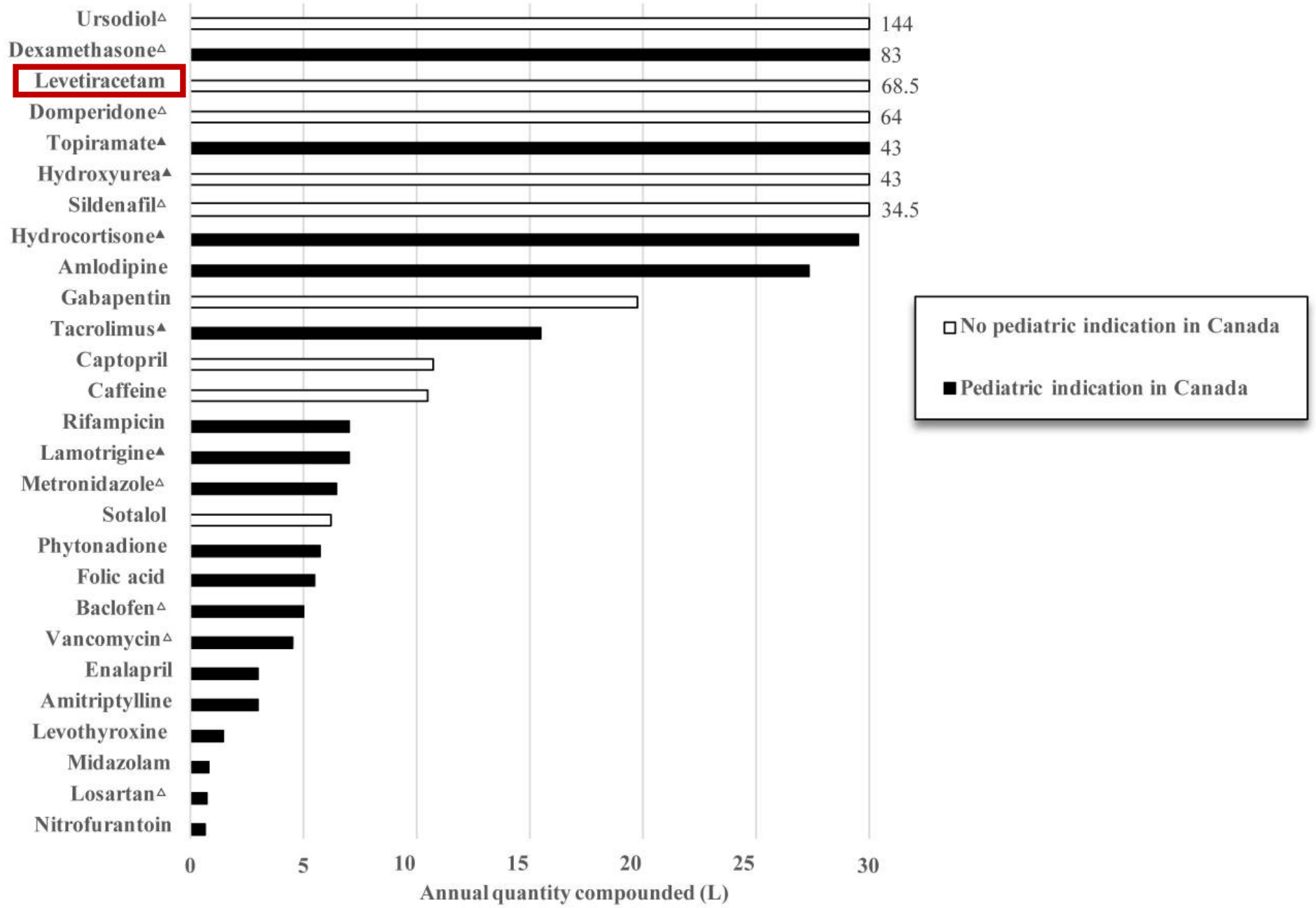
New drugs

Old, off-patent drugs

Martin 2018


NDC 0121-0799-16
Levetiracetam
Oral Solution USP
100 mg/mL
PHARMACIST: Dispense the attached Medication Guide to each patient.
Rx ONLY
16 fl oz (473 mL)
pai Pharmaceutical Associates, Inc.
Greenville, SC 29605
DURA-DOSE
Delivers 5 mL
NDC 0121-4799-05
Levetiracetam
Oral Solution, USP
500 mg/5 mL
(01) 0 0301214 79905 7
Rx ONLY
FOR INSTITUTIONAL USE ONLY
PHARMACEUTICAL ASSOCIATES, INC.
Greenville, SC 29605
SEE INSERT
Delivers 10 mL
NDC 0121-1598-10
Levetiracetam
Oral Solution, USP
1,000 mg/10 mL
(01) 0 0301211 59810 3
Package Not Child-Resistant
Rx ONLY
PHARMACEUTICAL ASSOCIATES, INC.
Greenville, SC 29605
SEE INSERT


1999
US approves tablets for adjunctive therapy of POS in adults
2003
Canada approves tablets for adjunctive therapy of POS in adults
EU approves tablets for adjunctive therapy of POS in adults
2000
US & EU approve oral solution for adjunctive therapy of POS in adults and children ≥ 4 years
2005



Litalien 2020

Compounding

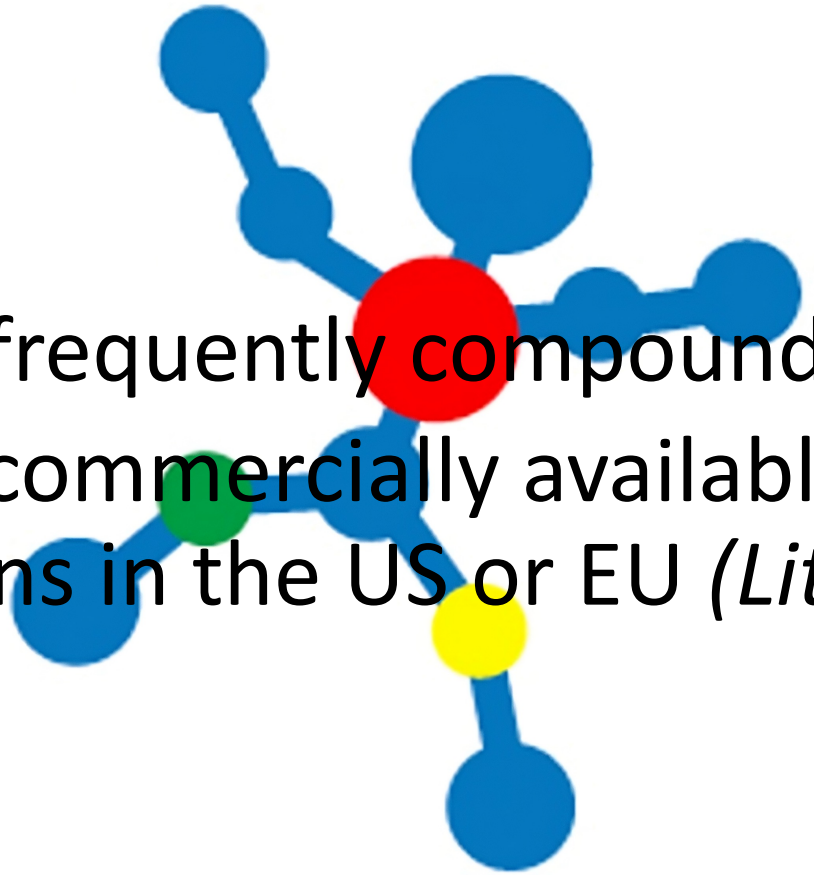
Extent of Problem in Canada

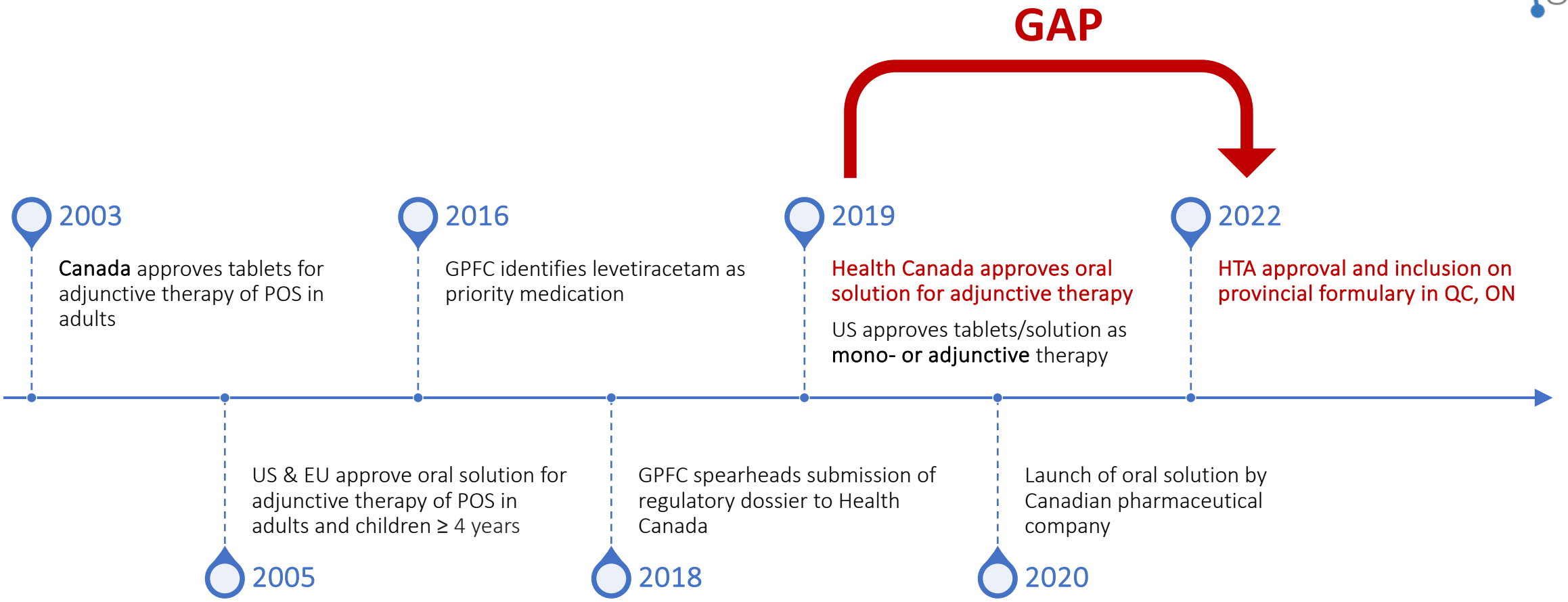
- 2007-2016: 60% of new drugs for children <6 years unavailable in child-friendly formulation *(Raja 2020)*
- CHUSJ *(Landry 2023)*:
  - ¼ enteral drugs compounded
  - ½ of hospitalized children prescribed at least one compounded drug
- Compounding errors → 35% of harmful medication incidents in children *(ISMP Canada 2022)*

news

Parents find son's lifeless body after pharmacy switches sleep medication for toxic dose of another drug

~50% of frequently compounded oral liquid medications are commercially available as child-friendly formulations in the US or EU *(Litalien 2020)*




GAP
2003
Canada approves tablets for adjunctive therapy of POS in adults
2005
US & EU approve oral solution for adjunctive therapy of POS in adults and children ≥ 4 years
2016
GPFC identifies levetiracetam as priority medication
2018
GPFC spearheads submission of regulatory dossier to Health Canada
2019
Health Canada approves oral solution for adjunctive therapy
US approves tablets/solution as mono- or adjunctive therapy
2020
Launch of oral solution by Canadian pharmaceutical company
2022
HTA approval and inclusion on provincial formulary in QC, ON

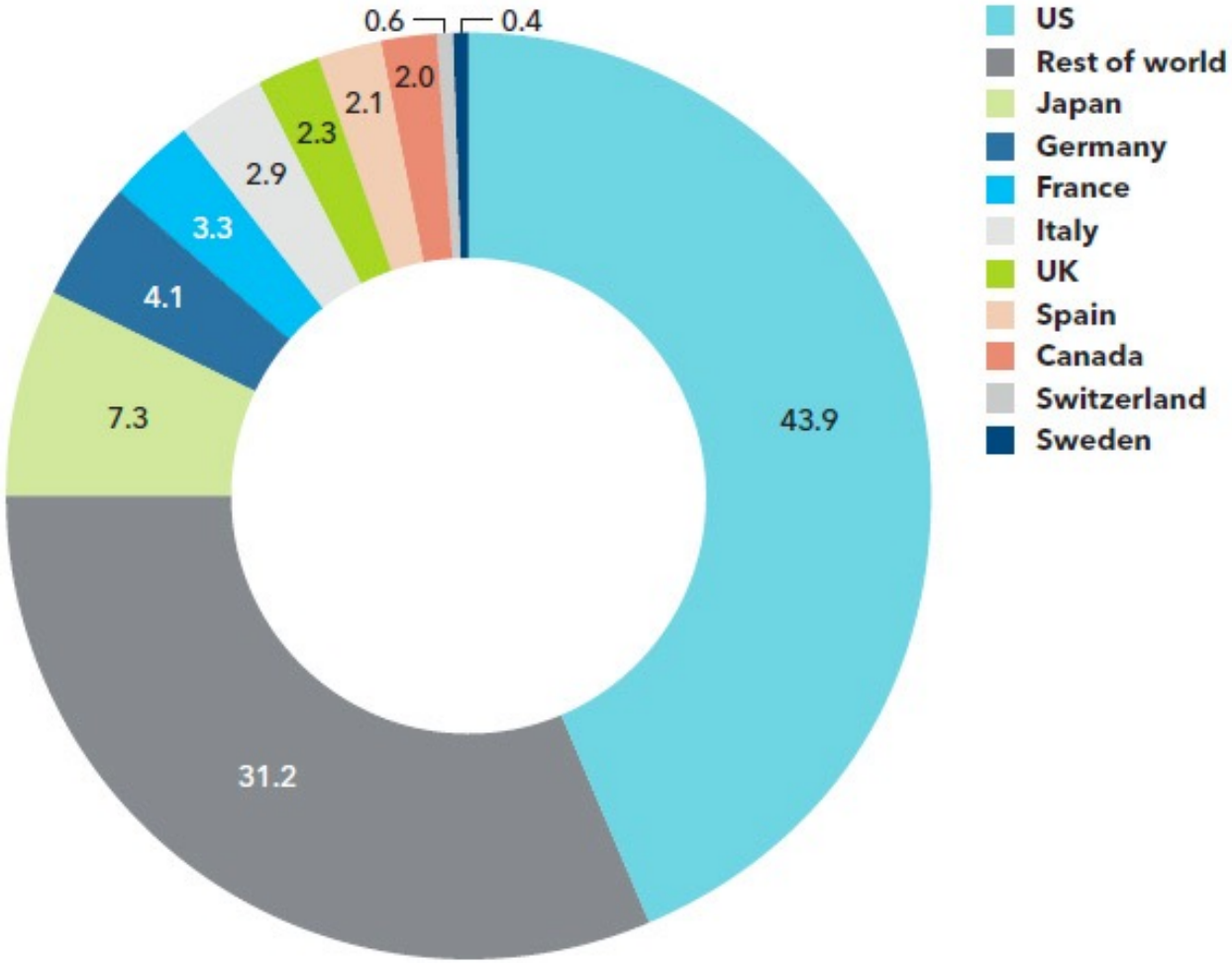
Canadian Challenges

- Fragmented reimbursement
  - Small market size
- Outdated regulatory framework
  - Lack of incentives

Fragmented Reimbursement

Small Market Size

- ~ 2% global market share
- pediatric drugs: <10%



Outdated Regulatory Framework

- USA:
  - 2002: Best Pharmaceutical for Children Act (BPCA)
  - 2003: Pediatric Research Equity Act (PREA)
  - 2005: FDA BPCA Pediatric Formulation Initiative
- EU:
  - 2007: EU Pediatric Regulation
  - 2007: pediatric-use marketing authorisation (PUMA)
  - 2007: European pediatric Formulation Initiative (EuPFI)
- WHO:
  - 2007: Make Medicines Child Size
  - 2016: Global Accelerator for pediatric Formulations (GAP-f)

REGULATION

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Raja 2020

Outdated Regulatory Framework

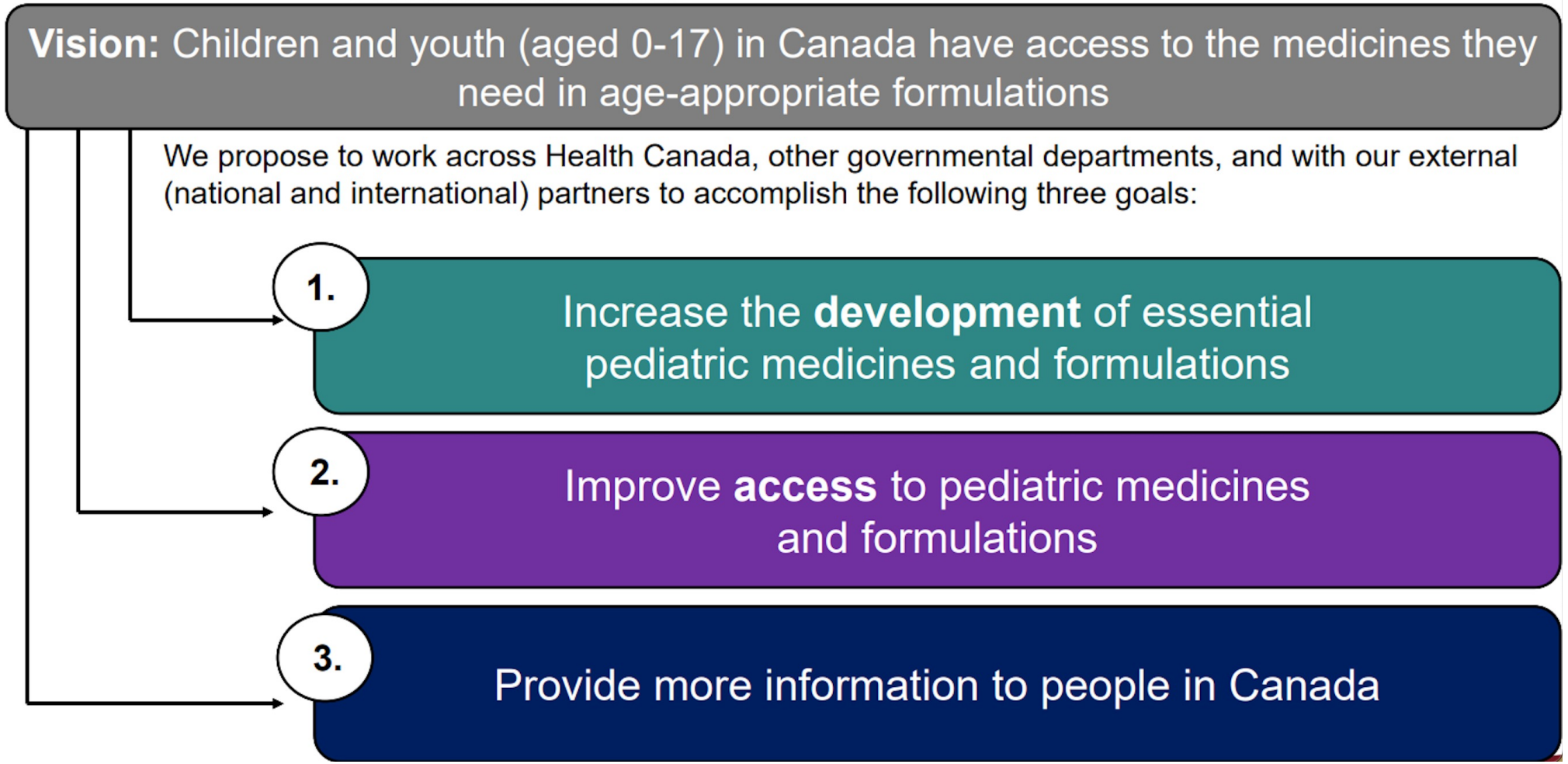
- Canada:
  - 2014 Improving Medicines for Children in Canada
  - 2016 GPFC
  - No pediatric rule
  - No trusted foreign review policy
  - No harmonization of regulations with other jurisdictions
  - No incentives for formulations for old, off-patent drugs
    - On-patent: 6-month market exclusivity, 8-year data protection

Sustainable change requires a pediatric-sensitive regulatory framework

Working Together for Regulatory Change

- Pediatric rule
  - Mandate pediatric safety & efficacy data
  - Pediatric indications and formulations
  - Data and market protection
- Trusted Foreign Decisions pathways
  - Reasonable market experience requirements
- Innovative fee structures
  - Reduced rates for pediatric medications
  - Accelerated review
  - Orphan drug designation/some form of protection for medication identified as meeting a critical need (NPLPD)

Pediatric Drug Action Plan



National Priority List of Pediatric Drugs

- "NPLPD"
- Main objective: scope unmet pediatric drug needs
  - Highlight drugs identified as urgently requiring commercialization or updated labelling
  - Pursue targeted engagement with industry partners to encourage NPLPD-specific drug submissions to Canada
  - Inform development of specific incentives and/or facilitated review pathways

NPLPD

Eligibility criteria have been set out as follows:

- Based on your experience, this drug address disease(s) / disease areas / conditions with high unmet need

AND

- To your knowledge, this drug currently lacks:
  a. Approval for sale in Canada; OR
  b. A pediatric indication (i.e. a drug that is currently marketed in Canada with only an adult indication and/or a pediatric indication limited to certain age groups); AND/OR
  c. A child-friendly formulation (i.e. a drug that is currently available in Canada only in a formulation designed for adults)

AND

- This drug is approved for sale in a trusted foreign jurisdiction with an established pediatric indication and/or child-friendly formulation (this criterion will be verified by Health Canada)

Total nominations

100s

Unique submissions

Redundant submissions

Unique + consolidated redundant

Eligible (screened in)

Not eligible (screened out)

New drug

New indication

New formulation

New indication AND new formulation

10s

Draft guidance document on submitting pediatric studies and pediatric development plans

- Pediatric study submission policy pilot
  - "… *may be used to inform future policy."*
- *"Health Canada will be requesting that sponsors filing a new drug submission (NDS) and certain supplements to a new drug submission (SNDS) include findings from pediatric studies."*
  - *"… submitted through the voluntary policy pilot program"*

Response letter

FDA initial Pediatric Study Plan (iPSP) or EMA Pediatric Investigation Plan (EU-PIP) accepted as Pediatric Development Plan (PDP)

Expedite the regulatory changes necessary to mandate the submission of PDPs and pediatric data in all drug submissions when pediatric use of a medication can be expected or anticipated.

Develop a comprehensive plan to communicate the details of the policy pilot to sponsors, including explicit references to: (1) the PDAP (in the overview section of the guidance document), and (2) existing incentives that can accompany participation in the pilot program.

Remove the exclusion for biosimilar drugs.

Remove the exclusion of third-party data submission pathways.

" And now, Mr. X will present our hidden agenda. "

New drug	New indication	New formulation	New indication AND new formulation
			

- Your experience with the “inventory of needs for pediatric medicines”?
- How to identify "high-yield" products?
- What do sponsors see as the greatest barriers/disincentives to bringing products to Canada?
- What incentives would have sponsors jumping to fill these unmet needs?

Our Team

Left to right: Denis Lebel, Sophie Bérubé, Hélène Roy, Ginette Piteau,
Dr. Catherine Litalien and Dr. Raphaël Kraus

Select References

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