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Drug Safety in P(a)ediatrics Shifting from Catching Up to Moving Forward

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Western

Division of Clinical Pharmacology

Conflict of Interest Disclosures

Dr. Michael Rieder

- I have had in the past 3 years, a financial interest, arrangement or affiliation with the following organizations that could be perceived as a direct or indirect conflict of interest in the content of this presentation.
  - CIHR-GSK Chair in Paediatric Clinical Pharmacology
  - President, Canadian Society of Pharmacology and Therapeutics
  - Member, Human Drug Advisory Panel, Health Canada
  - Member, Drug Therapy Committee, Canadian Paediatric Society
  - Editorial Board, *Paediatrics and Child Health, British Journal of Clinical Pharmacology*

Objectives

- Expert
  - to describe the burden of adverse drug reactions in children
  - to identify risk factors for adverse drug reactions and how they apply to specific groups of children
- Scholar
  - to identify new directions in the evaluation and diagnosis of adverse drug reactions
  - to identify new trends in therapeutics and their potential impact on adverse drug reactions


North Pole
Norwegian Sea
Norway
Polar Ice
Greenland Sea
UK
Russia
Arctic Ocean
Ellesmere Island
Alert
Kalaallit Nunaat (Grønland) (Denmark)
Iceland
North Magnetic Pole
Bering Strait
Arctic Circle
Beaufort Sea
Banks I
Resolute
Baffin Bay
Alaska (USA)
Inuvik
Victoria Island
Gjoa Haven
Baffin Island
Davis Strait
Dawson
Great Bear Lake
Mackenzie River
Yukon Territory
Whitehorse
Northwest Territories
Nunavut
Iqaluit
Labrador Sea
Atlantic Ocean
Yellowknife
Baker Lake
Ungava Bay
Fort Nelson
Great Slave Lake
CANADA
Nain
Newfoundland
British Columbia
Fort McMurray
Kuujjuaq
Hudson Bay
Churchill Falls
St John's
Prince George
Alberta
Churchill
Pacific
Edmonton
Manitoba
L. Winnipeg
La Grande Rivière
Sept-Îles
Saint-Pierre et Miquelon (France)
Vancouver
Fraser River
Kamloops
Calgary
Saskatchewan
Sandy Lake
James Bay
Quebec
Prince Edward Island
Charlottetown
Victoria
Saskatoon
Ocean
Regina
Winnipeg
Thunder Bay
Ontario
New Brunswick
Québec
Nova Scotia
Halifax
Fredericton
Montréal
LEGEND
United States of America
Lake Superior
Ottawa
Atlantic Ocean
National capital
Provincial or Territorial capital
Other populated places
Toronto
Lake Michigan
Lake Huron
Lake Ontario
London
International boundary
Provincial or Territorial boundary
Lake Erie
Scale
Exclusive 200 nautical mile Economic Zone (EEZ)
300 0 300 600 900
km
km
© 2001. Her Majesty the Queen in Right of Canada, Natural Resources Canada.

Western

"Pediatrics does not deal with miniature men and women, with reduced doses and the same class of diseases in smaller bodies, but ... it has its own independent range and horizon and gives as much to general medicine as it receives from it"

- Abraham Jacobi, 1889

The Ideal Medication

- Effectively treats or prevents disease
- Has no adverse events

The reality

- Drugs are never safe and effective in all patients
- Variability in patient response can have serious consequences

Context

- Drug use in children
- Myths
  - Drugs are not commonly used in the care of children
  - When they are used, antibiotics are essentially the only drugs used

Some Inconvenient Truths

- Perception - Rare
- Fact - Common
  - In an average year, the average Canadian child is prescribed 3.9 prescriptions; the average US child 3.6 prescriptions in a year
    - Paed Child Health 2003; 8 Suppl A
- Perception - Only antibiotics
- Fact - Many drugs/drug classes
  - Among a cohort of 1,000,000 Canadian children in a year, more than 1,200 different drugs were prescribed
    - Paed Child Health 2003; 8 Suppl A

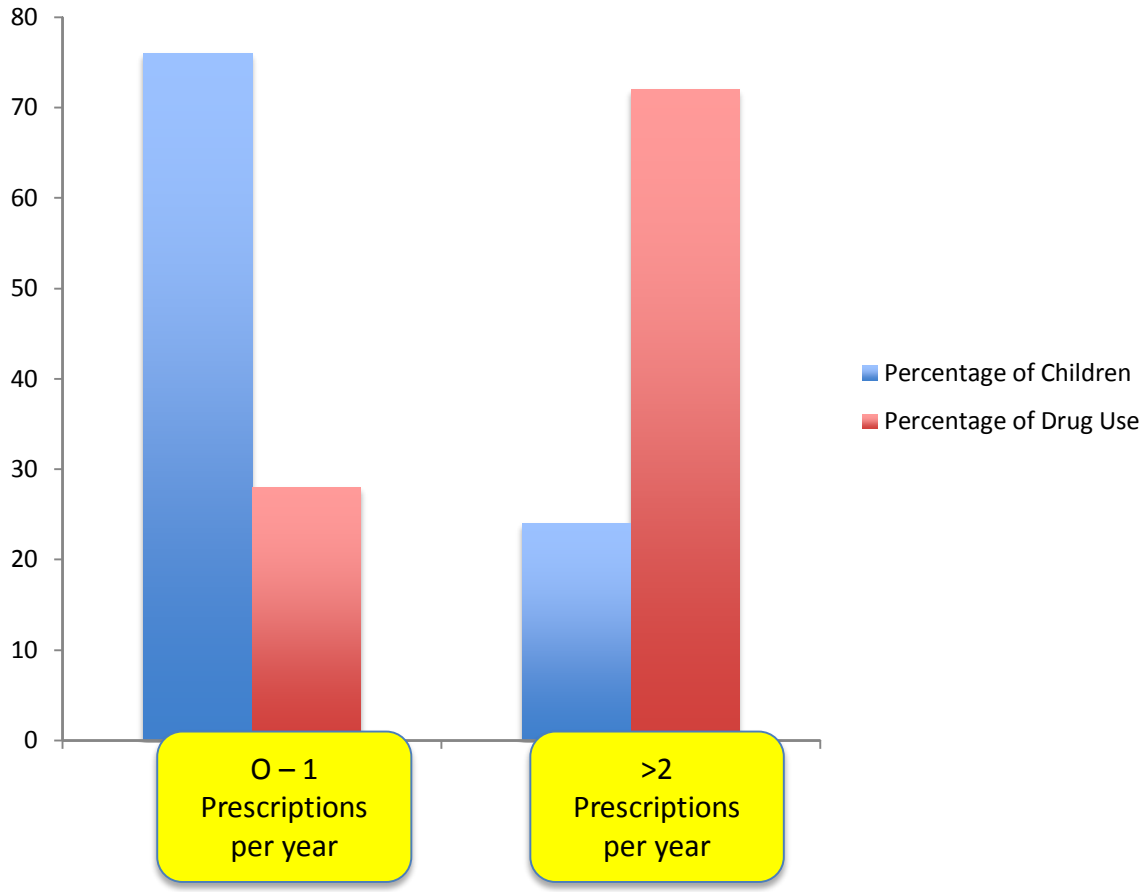
	Both sexes				Male			
Under 18 years	20.5	23.8	24.7	23.5	2.4	4.1	4.0	3.6
18–44 years	31.3	35.9	37.4	38.1	5.7	8.4	10.6	9.6
45–64 years	54.8	64.1	65.2	67.2	20.0	30.8	35.3	34.7
65 years and over	73.6	84.7	89.4	89.8	35.3	51.8	62.9	64.8

CDC Data 2015

TABLE 1
Distribution of claimants and prescriptions and number of prescriptions per claimant for selected therapeutic areas

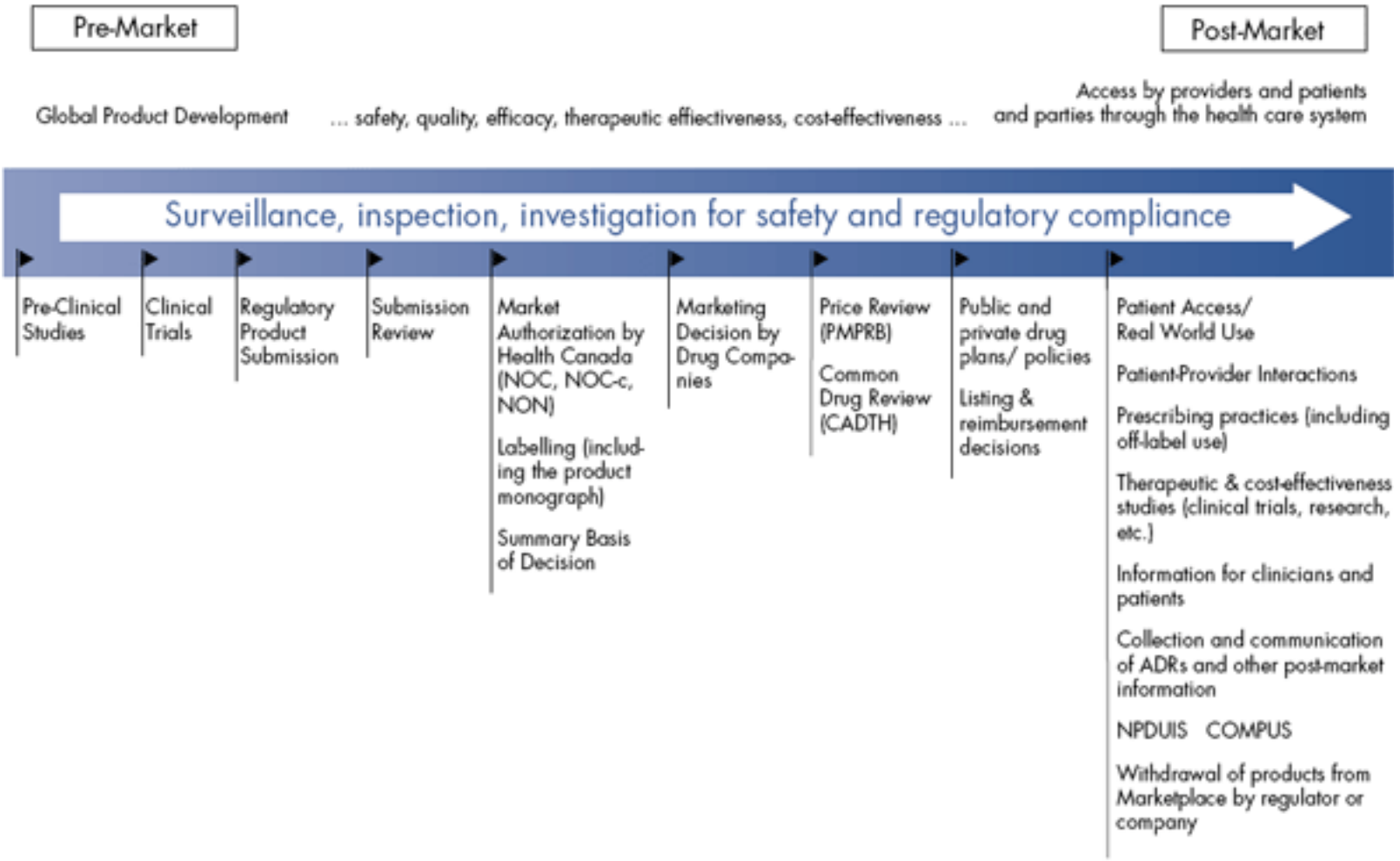
Therapeutic class	Distribution of claimants		Distribution of prescriptions		Prescriptions per claimant
	Number of Claimants	Share of total claimants	Number of prescriptions	share of total prescriptions	
Antibiotics	780,684	76%	1,740,446	43%	2.2
Respiratory drugs	182,271	18%	522,216	13%	2.9
Analgesics and anti-inflammatory drugs	84,024	8%	116,005	3%	1.4
Acne drugs	72,504	7%	223,700	6%	3.1
Contraceptives	40,512	4%	194,796	5%	4.8
Stimulants	33,882	3%	161,184	4%	4.8
Antidepressants	16,731	2%	64,929	2%	3.9
Antipsychotic agents	3,873	0.4%	20,023	0.5%	5.2
Anti-convulsant agents	6,409	0.6%	46,261	1%	7.2
Gastrointestinal agents	16,267	2%	40,299	1%	2.5
Antidiabetic drugs	3,583	0.3%	41,682	1%	11.6
All drugs (total)	1,031,731	100%	4,028,502	100%	3.9

The sum of claimants by therapeutic class exceeds the total 1.03 million claimants because some claimants were dispensed drugs from more than one therapeutic class

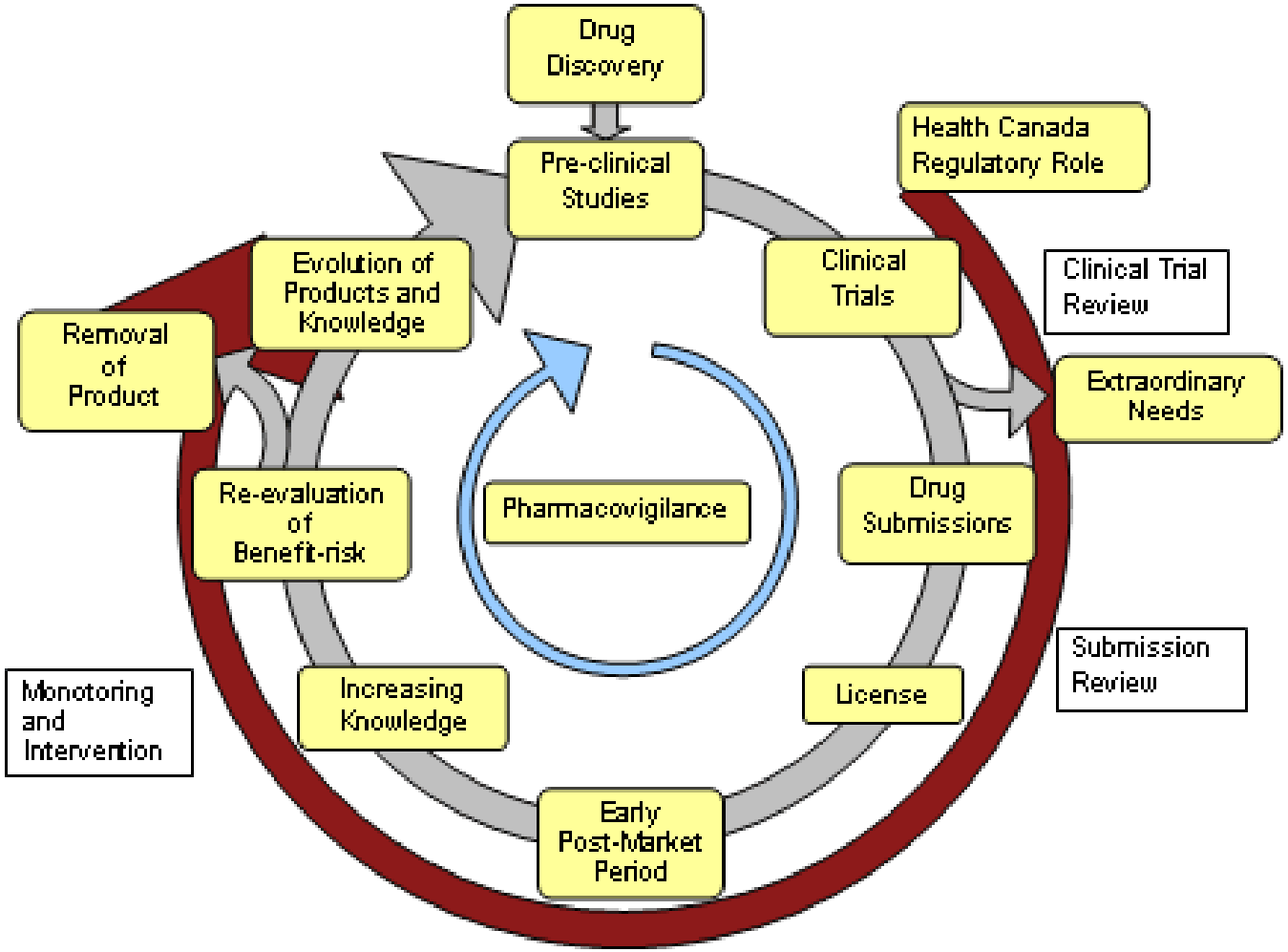

80
70
60
50
40
30
20
10
0
O – 1 Prescriptions per year
>2 Prescriptions per year
Percentage of Children
Percentage of Drug Use

Double Edged Sword

- A blade with two sharp edges
- A term used to describe a situation in which good or bad effects
- Roots from Arabic (sayf ḏū ḥadayn, “double-edged sword”) and Biblical origins as to the Word of God (Hebrews 4:12)” Sharper than any double-edged sword, it penetrates even to dividing soul and spirit, joints and marrow”
- Applies to the beneficial and adverse effects of medication (*NEJM)*


Pre-Market
Post-Market
Global Product Development
... safety, quality, efficacy, therapeutic effiectiveness, cost-effectiveness ...
Access by providers and patients and parties through the health care system
Surveillance, inspection, investigation for safety and regulatory compliance
Pre-Clinical Studies
Clinical Trials
Regulatory Product Submission
Submission Review
Market Authorization by Health Canada (NOC, NOC-c, NON)
Labelling (includ-ing the product monograph)
Summary Basis of Decision
Marketing Decision by Drug Compa-nies
Price Review (PMPRB)
Common Drug Review (CADTH)
Public and private drug plans/ policies
Listing & reimbursement decisions
Patient Access/ Real World Use
Patient-Provider Interactions
Prescribing practices (including off-label use)
Therapeutic & cost-effectiveness studies (clinical trials, research, etc.)
Information for clinicians and patients
Collection and communication of ADRs and other post-market information
NPDUIS COMPUS
Withdrawal of products from Marketplace by regulator or company

Life-Cycle of Product and Knowledge



Paradox of Drug Development and EBM

1. Clinical trials provide evidence of efficacy and safety at <u>usual doses</u> in *populations*

+  = Efficacious & Safe

2. Physicians treat *individual* patients who can <u>vary widely</u> in their response to drug therapy

+  =

- No Response
- Efficacious & Safe
- Adverse Drug Reaction

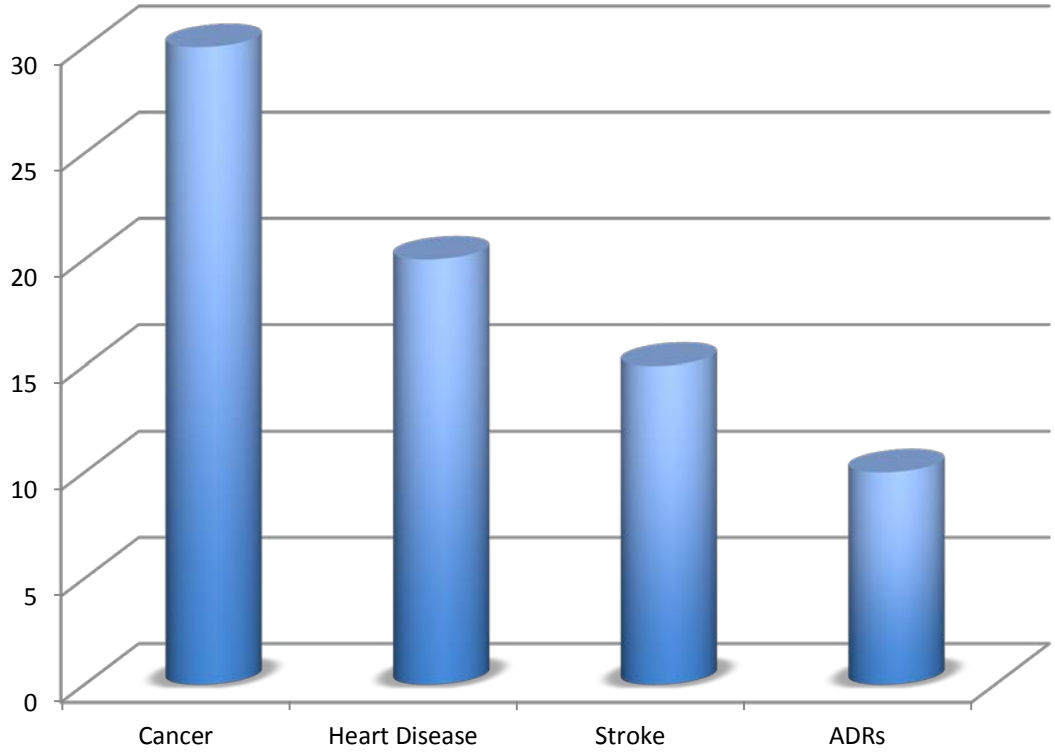
An ADR is an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dose regimen, or withdrawal of the product

- Edwards and Aronson (2000), *Lancet*, 356(9237):1255-1259

Adverse Drug Reactions

- **4th** leading cause of death in the USA[1]
- Health care costs: $137-177 billion annually (USA)[2-3]
- Cause **7%** of all hospital admissions[4]
- Cause serious reactions in over 2,000,000 hospitalized patients (6.7%) each year in the USA[1]
- Cause fatal reactions in over 100,000 hospitalized patients each year in the USA[1]
- **95%** of all ADRs are unreported

1. Lazarou et al, *JAMA*, 1998
2. Johnson et al, *Arch Intern Med* 1995
3. Ernst et al, *J. Am. Pharm. Assoc.* 2001
4. Pirmohamed et al, *BMJ*, 2004
5. MjoÈrndal et al, EACPT3, 1999



Yet nowhere is this reported

Why?

Nosology

- 6 year old child presents with nephroblastoma; following surgery undergoes chemotherapy including ifosfomide
- During chemotherapy it is noted that there is evidence of renal injury including aminoaciduria
- Over the next 10 years following therapy there is no evidence of tumour recurrence

- During these 10 years there is progressive decline in renal function to the point where dialysis is needed
- While waiting renal transplant the patient expires of complications of end-stage renal failure
- Cause of Death?

Nephroblastoma

- This seems somewhat paradoxical as the tumour had been, by all accounts, successfully eradicated
- It would be reasonable to assume that the treated team of oncologists did not desire or plan for this outcome
- This nosological anomaly is one of the reasons that ADRs are under-estimated in their impact on child health
  - *N Engl J Med* 2006; 355:1522-1523

Cultural Issues

Risk Factors for ADRs

- History of a previous ADR
- Large drug doses
- Polypharmacy
- Impairment of the organs of excretion (hepatic or renal dysfunction)
- Extremes of age
- Female sex
- Specific genetic polymorphisms
- General Anaesthesia
    - *Pediatr Clin North Am* 2012

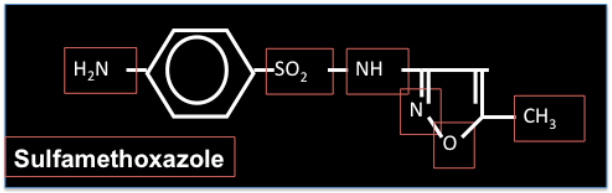
Are ADR Rates in Children Difference than those in Adults?

- Has been relatively little data with respect to ADRs in children compared to adults
- What data is present suggests that overall rates may be similar
- In some circumstances, controversy as to whether risks may be lower or in fact may be higher; despite the impression, when actual data is reviewed risks are never lower and often higher
- In some groups of children and for some conditions, the risk of an adverse drug event is nearly 100%
  - *BMC Med* 2013 Nov 7;11:237
  - *Clin Pharmacol Ther* 2017 Mar 13. doi: 10.1002/cpt.677

Drug Safety

- For many years pharmacovigilence was conducted using passive surveillance involving data capture by regulatory agencies
- This approach resulted in serious adverse events being recognized by regulatory authorities many years after they had been recognized in the peer reviewed literature
- This approach also is associated with serious under-reporting of adverse drug events

Tragedies Over Time



Pemoline Induced Hepatic Injury

- Pemoline is a CNS stimulant used in the therapy of ADHD
- Entered the US market in 1975
- Withdrawn 30 years later
- However, an active search of the literature clearly demonstrated increased risk for hepatic injury – as early as 1978
  - *Drug Safety* 2008;31(2):169-80.

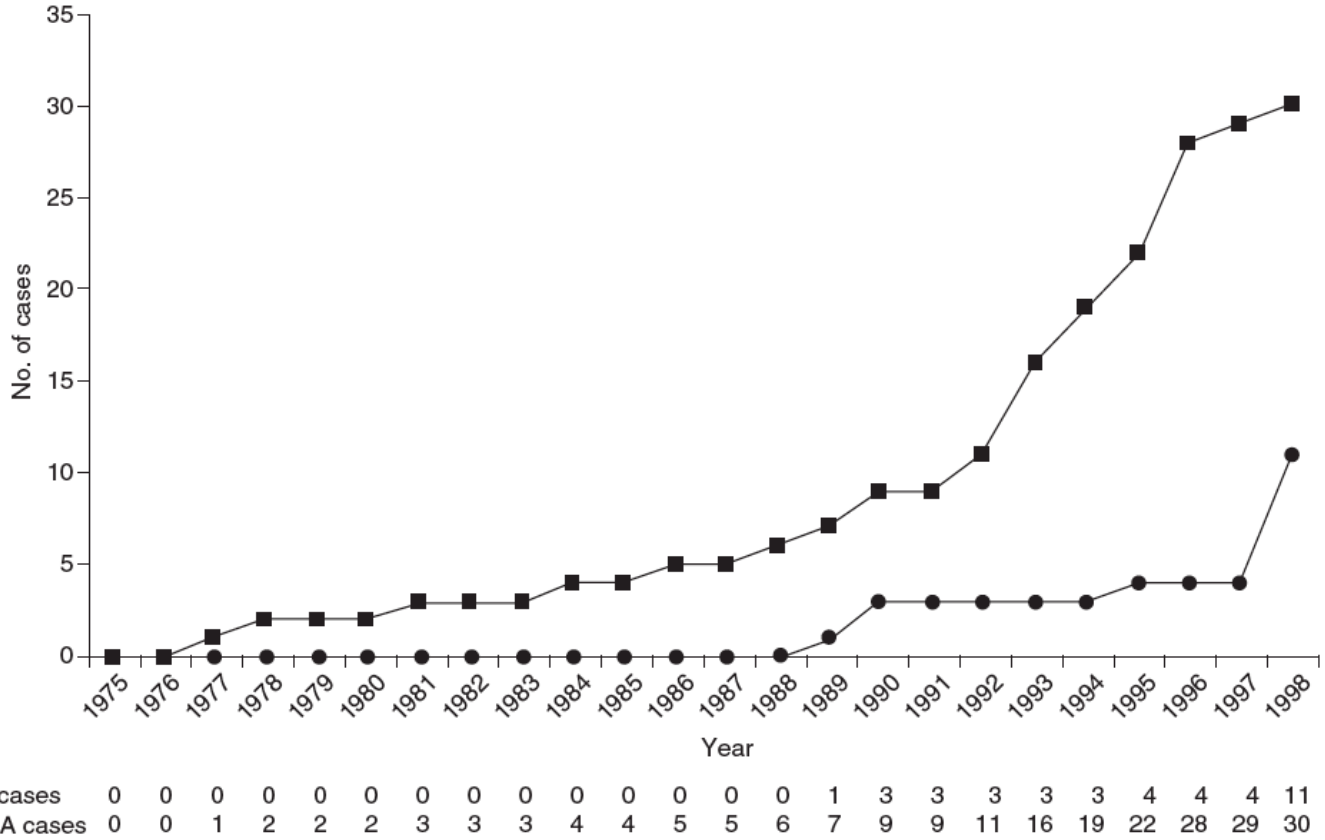
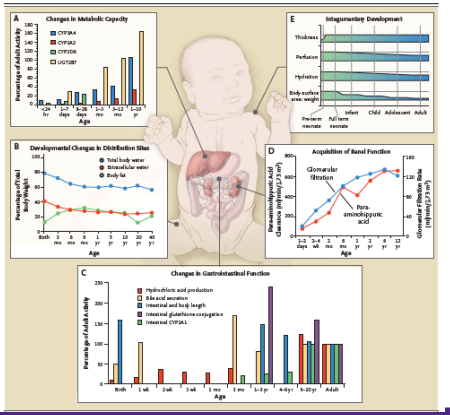


Fig. 1. Cumulative chart of children developing acute liver failure after receiving pemoline (cases from the US FDA and the medical literature for the period 1975–98).

Progress Over Time

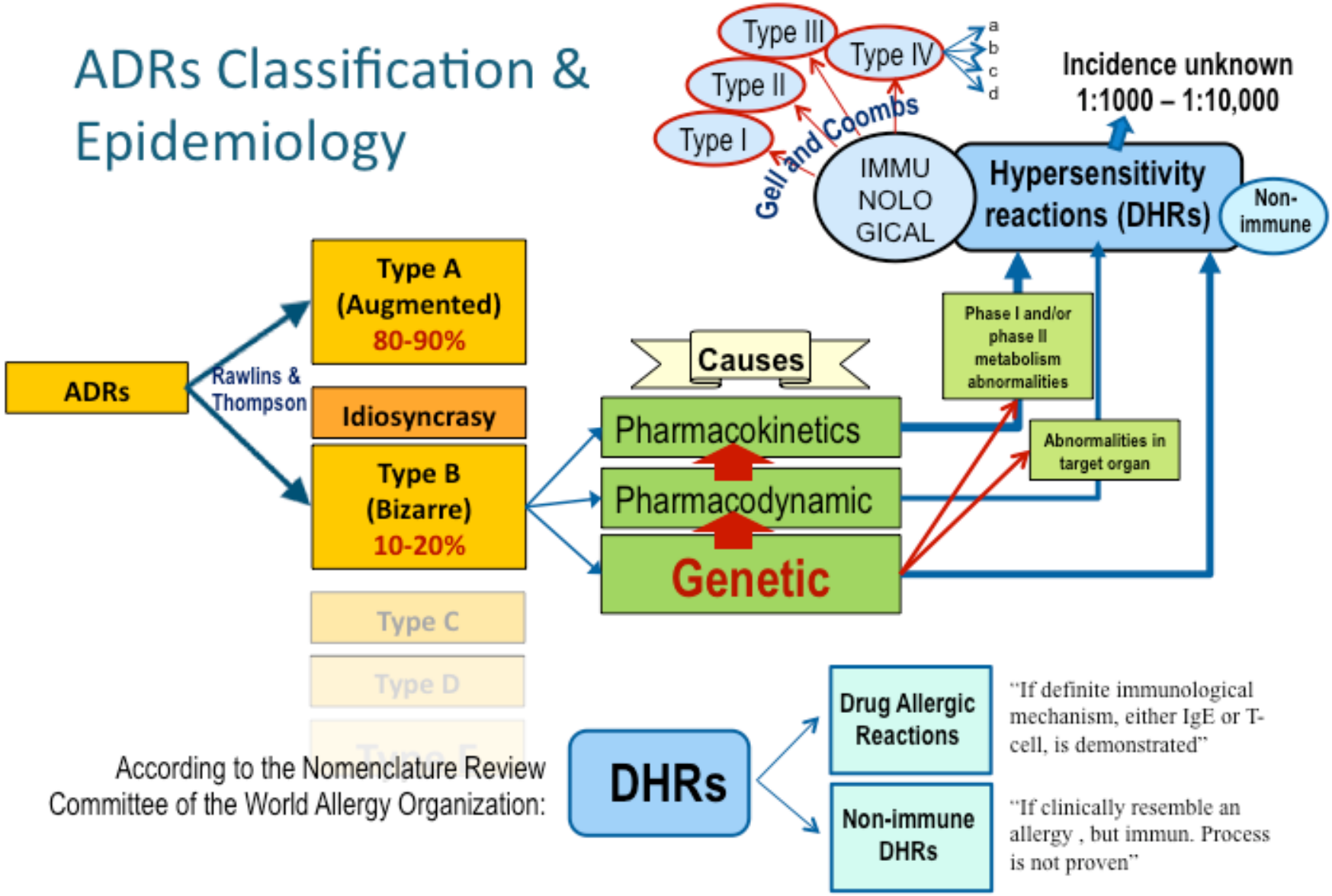
- There has been slow but steady progress on improving drug dosing and drug safety in children, largely in the area of dosing and largely driven by academic investigators and enhancing our understanding of developmental pharmacology
  - Once-daily gentamicin in NICU
  - Identification of unique risks in children
    - Valproic acid hepatotoxicity
    - Cefaclor serum sickness like reactions
      - *Drug News & Perspectives* 2010, 23(7)



At-Risk Populations

- Neonates, especially premature neonates
- Children with cancer
- Children with complex chronic disease
- Children in the PICU
- Toddlers
  - *Eur J Clin Pharmacol* 2012;68(5):801-10

ADRs Classification & Epidemiology



Special Cases in Children

- Drug Substitution
- 10 fold errors
  - Unique problem in Paediatrics
  - More common among certain staff
  - May be addressed by EMRs
- Drug Errors
  - Probably more common in children than adults
  - Again, may be more common among certain staff
  - May be addressed by EMRs but there is no data that EMRs actually make drug therapy safer for children

Special Issues

- Much of the ADR literature in children has focused on adverse events related to ontogeny
- It is well appreciated that premature infants are at a substantially increased risk for adverse events compared to older children and adults
- What is less appreciated is that some activation-induced events occur at substantially higher rates in toddlers and pre-school children
  - *Clin Pharmacol Ther* 2017 Mar 13. doi: 10.1002/cpt.677

Off-Label Use

- Many studies on off-label/unlicensed use of drugs in children
- Almost all of them are incidence or utilization studies
- Off-label drug use is actually quite common, even among adults
- However, off-label drug use in adults is often guided by evidence

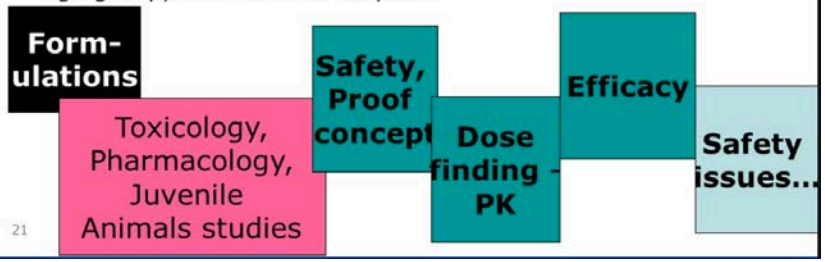
Table 5 **ADR risk factors assessed by multivariate analysis**

Covariate		HR (95% CI)	p-value
Gender	**Female**	1	0·152
	Male	0·896 (0·770, 1·042)	
Age on admission (years)		1·036 (1·021, 1·052)	<0·001
Received a GA	**No**	1	<0·001
	Yes	5·295 (4·417, 6·349)	
Oncology	**No**	1	0·655
	Yes	0·926 (0·661, 1·298)	
Number of authorised medicines		1·217 (1·171, 1·263)	<0·001
Number of off-label and/or unlicensed medicines		1·267 (1·201, 1·336)	<0·001
Number of uncategorised medicines		1·138 (0·969, 1·338)	0·116

Paediatric Investigation Plans

Data on efficacy, safety and quality (formulation, dosage form), Timelines (ref ICH guideline E11)

In practice, discussion on potential paediatric use and unmet needs to decide on the development and formulation for each age group, from birth to 18 years



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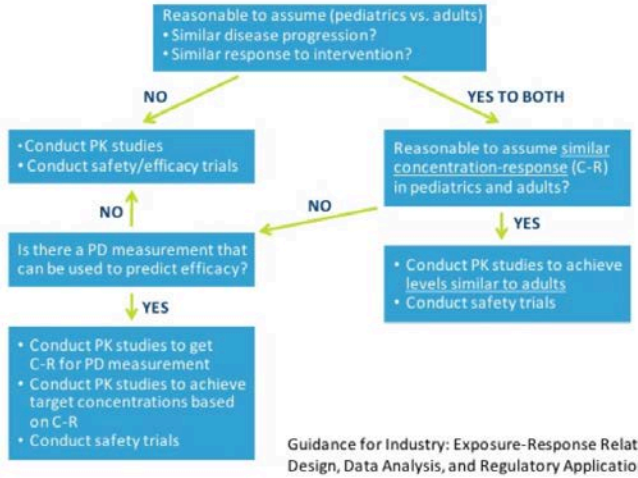
FDA Guidance for Pediatric Studies

Pediatric Study Decision Tree - Integration of PK-PD



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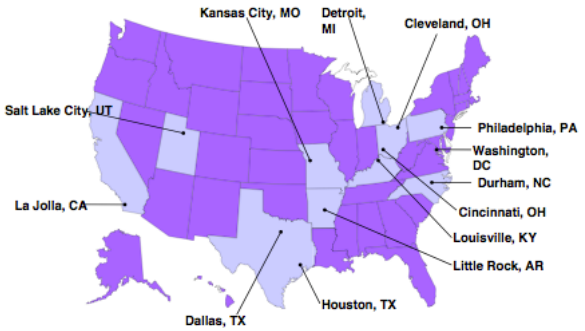
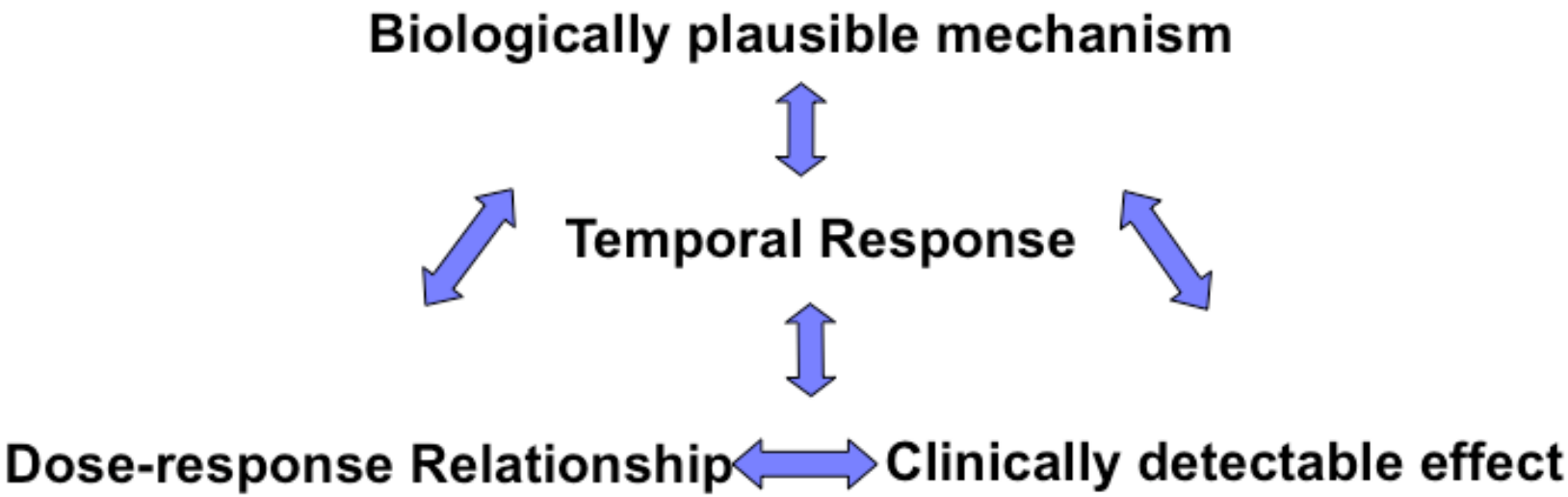
Guidance for Industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications, April 2003.

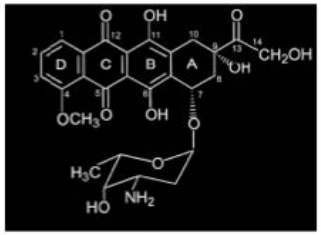
Pediatric Pharmacology Research Network (PPRU)

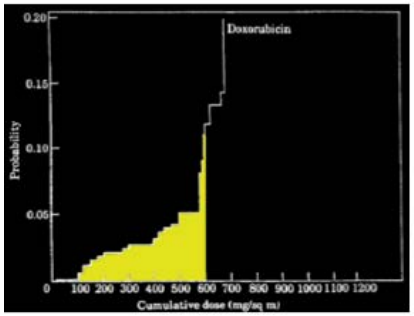


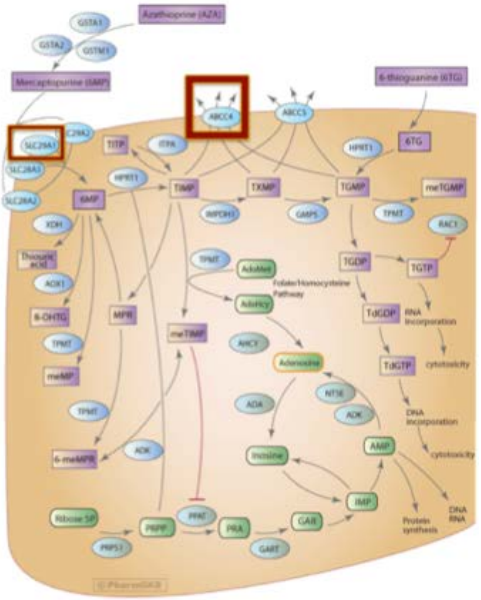
ADR Case Detection



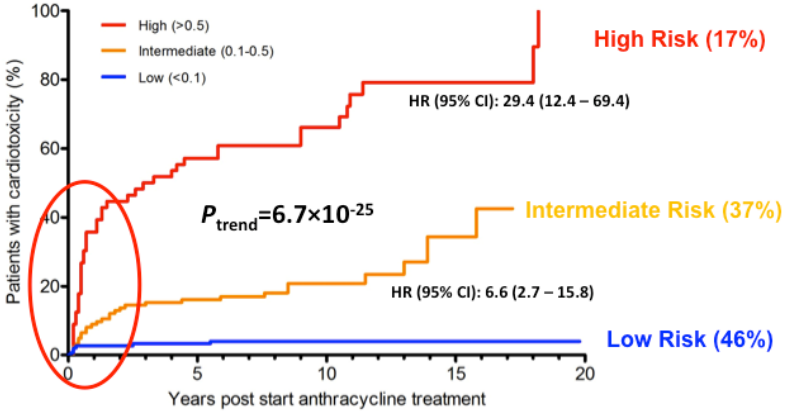
- **ADR Probability**
  - -possible, probable, definite (using WHO scale)
  - -Naranjo scale







Cardiotoxicity highest in first year but continues to increase over time in high risk groups



J Clin Oncol 2012 May 1;30(13):1422-8

NATURE GENETICS | LETTER

日本語要約

A coding variant in *RARG* confers susceptibility to anthracycline-induced cardiotoxicity in childhood cancer

Folefac Aminkeng, Amit P Bhavsar, Henk Visscher, Shahrad R Rassekh, Yuling Li, Jong W Lee, Liam R Brunham, Huib N Caron, Elvira C van Dalen, Leontien C Kremer, Helena J van der Pal, Ursula Amstutz, Michael J Rieder, Daniel Bernstein, Bruce C Carleton, Michael R Hayden, Colin J D Ross & The Canadian Pharmacogenomics Network for Drug Safety Consortium

Affiliations | Contributions | Corresponding author

Nature Genetics **47**, 1079–1084 (2015) | doi:10.1038/ng.3374
Received 25 December 2014 | Accepted 10 July 2015 | Published online 03 August 2015

Figure 1: A pharmacogenetic association with susceptibility to ACT is situated in *RARG*.

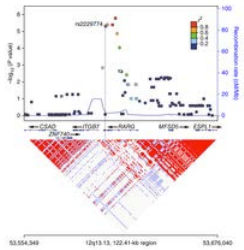
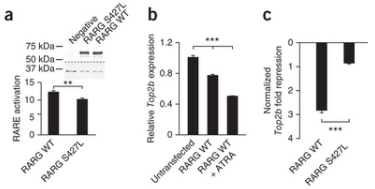


Figure 2: Functional characterization of RARG Ser427Leu identifies impaired transcriptional regulation.



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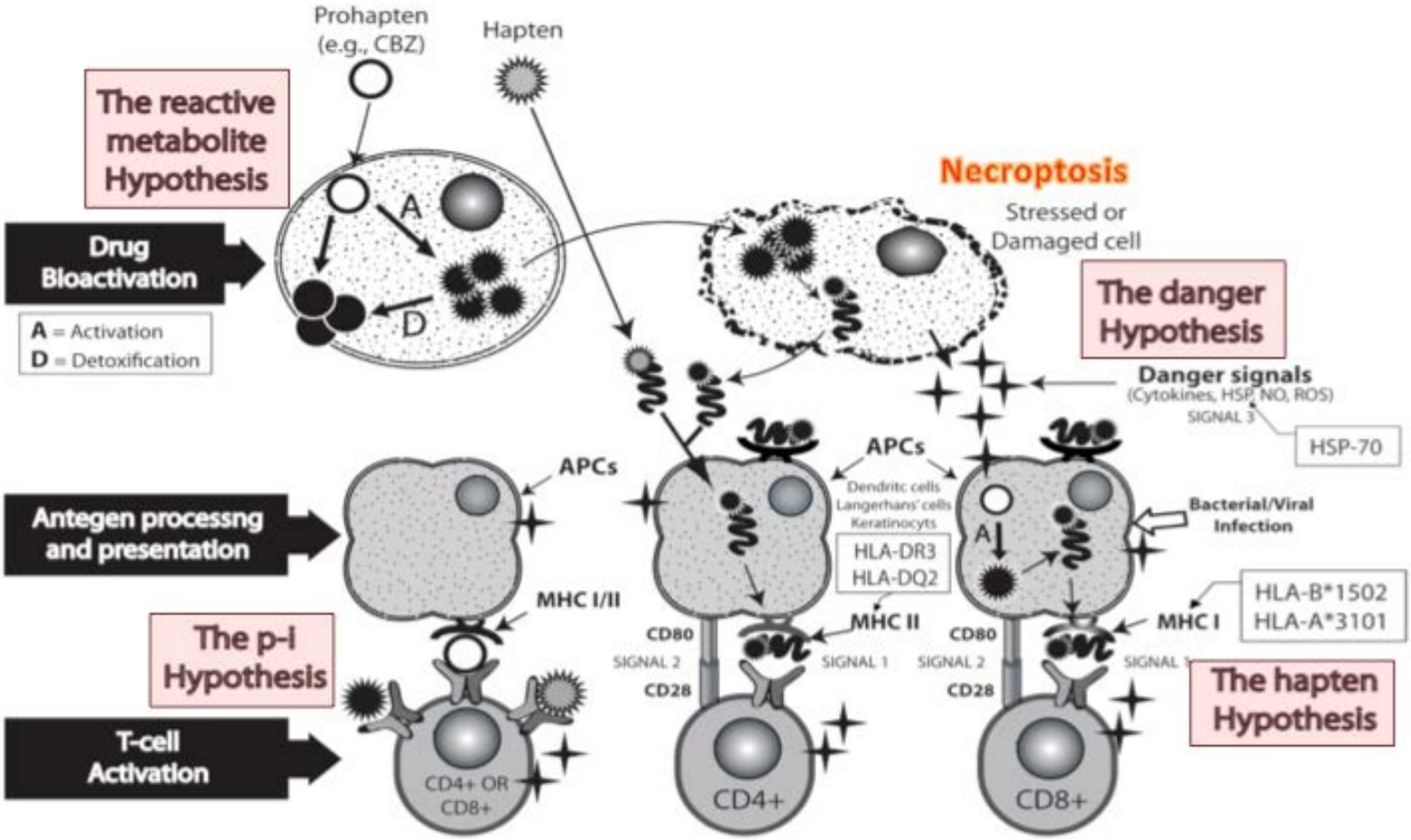
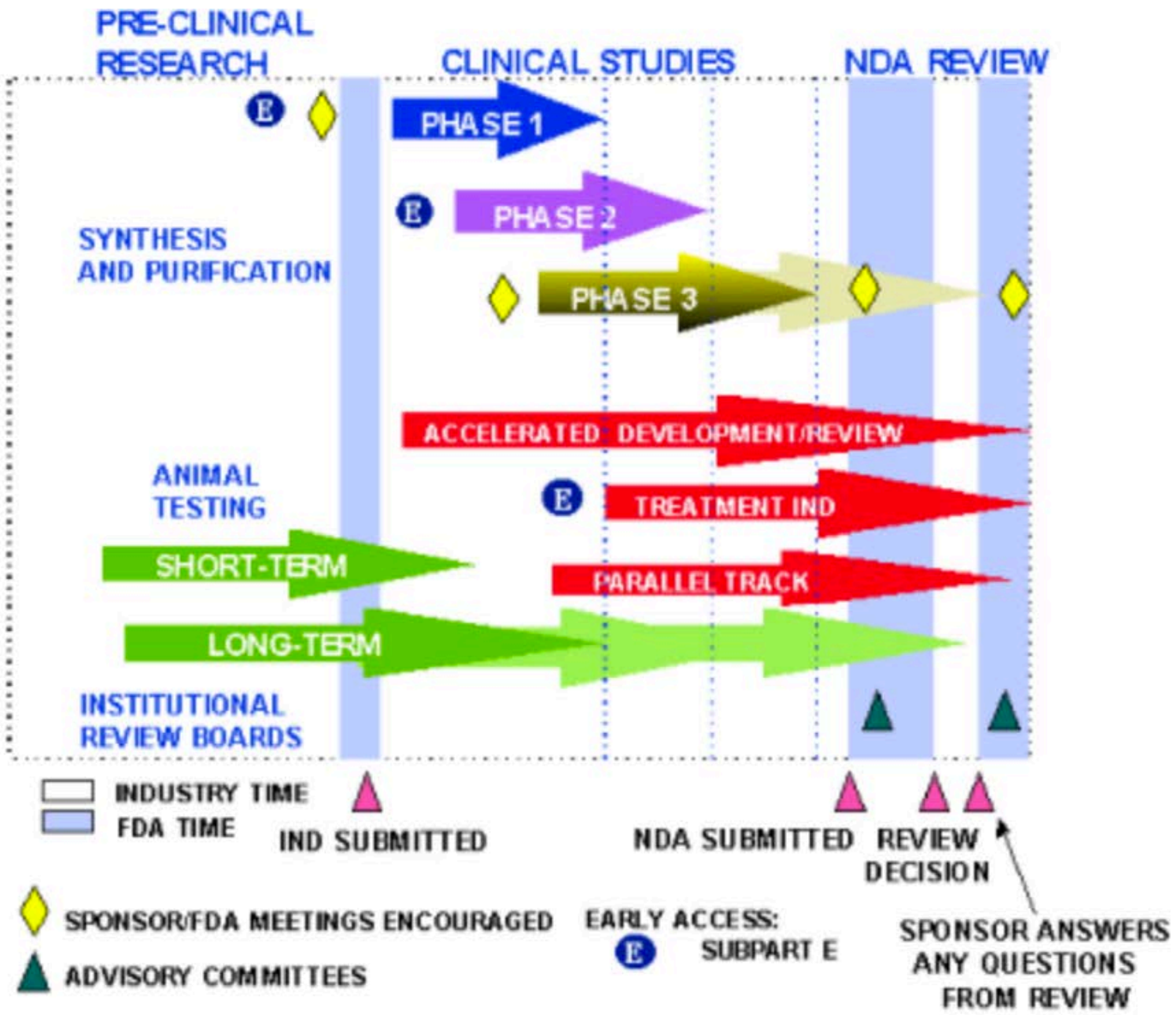
Pathophysiology of DHRs – The Reactive metabolite Hypothesis



Modified from: Elzagallaai et al., J Popul Ther Clin Pharmaco, 2011


PRE-CLINICAL RESEARCH
CLINICAL STUDIES
NDA REVIEW
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PHASE 2
SYNTHESIS AND PURIFICATION
PHASE 3
ACCELERATED DEVELOPMENT/REVIEW
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LONG-TERM
INSTITUTIONAL REVIEW BOARDS
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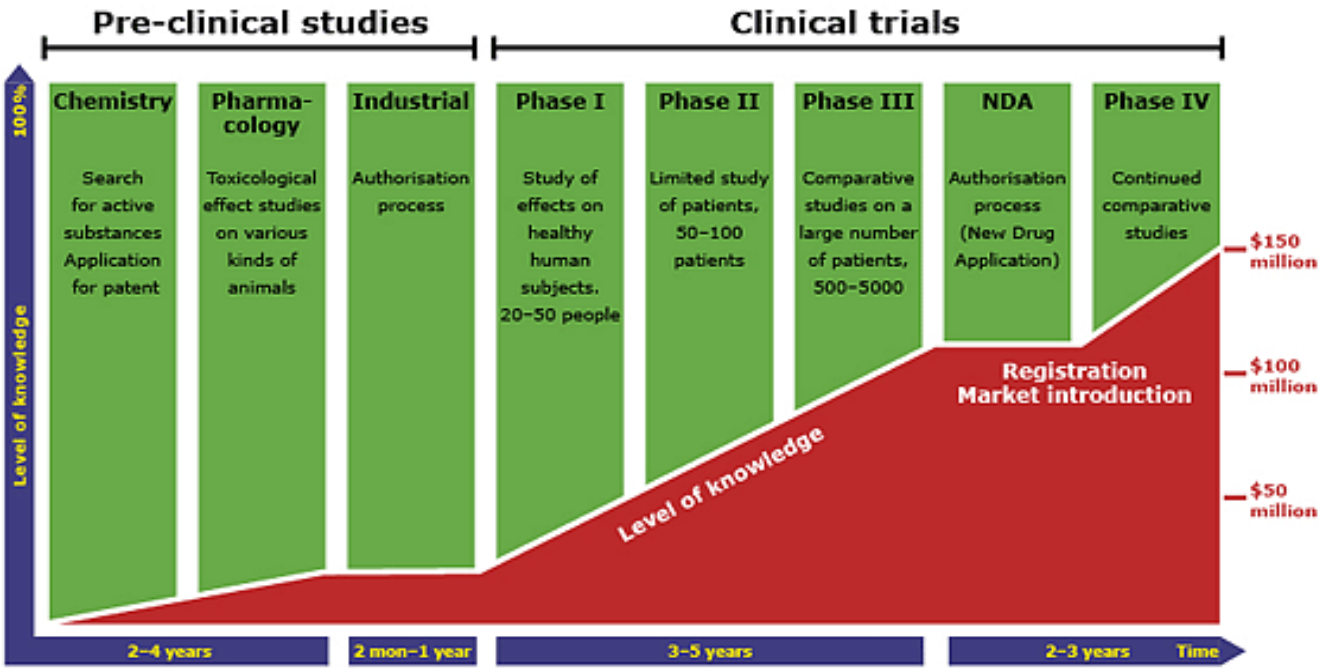
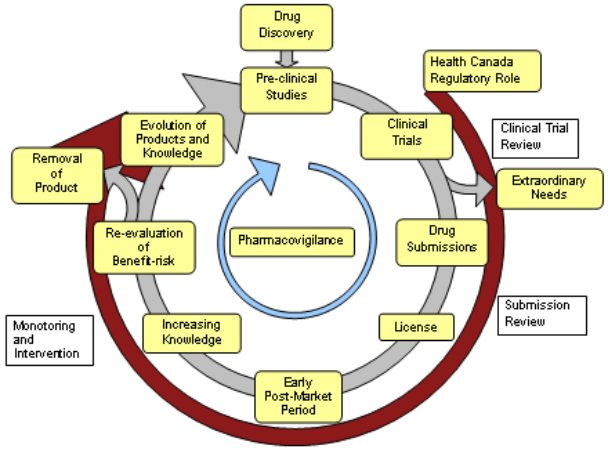
IND SUBMITTED
NDA SUBMITTED
REVIEW DECISION
SPONSOR/FDA MEETINGS ENCOURAGED
EARLY ACCESS:
E
SUBPART E
SPONSOR ANSWERS ANY QUESTIONS FROM REVIEW
ADVISORY COMMITTEES

TABLE 6
Rate of use of the new drugs in the therapeutic area for both paediatric and adult claimants

Drug	Rate per 1000 active claimants	
	Paediatric Claimants	Adult Claimants
Celecoxib	27	210
Citalopram	59	93
Rofecoxib	17	207
Bupropion	85	162
Montelukast sodium	49	45
Formoterol fumarate	4	19
Levofloxacin	1	10
Tazarotene	6	10
Zarfirlukast	2	14



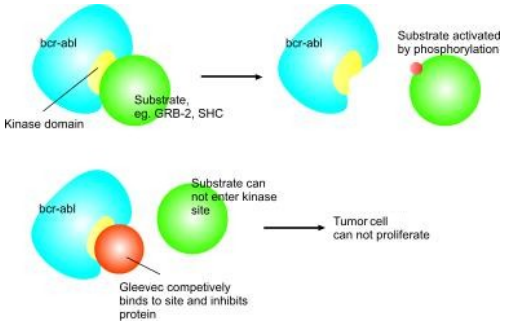
Life-Cycle of Product and Knowledge

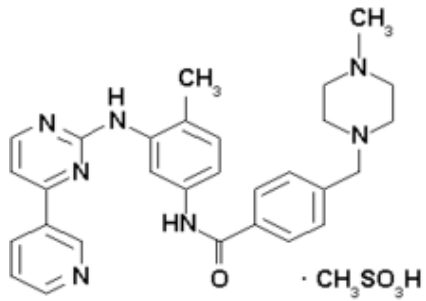


Big Data in Life Sciences*

*This and the following nine slides contributed by Edward Currie, AVP Life Sciences, Infosys

The Future


bcr-abl
Kinase domain
Substrate,
eg. GRB-2, SHC
bcr-abl
Substrate activated
by phosphorylation
bcr-abl
Substrate can
not enter kinase
site
Tumor cell
can not proliferate
Gleevec competively
binds to site and inhibits
protein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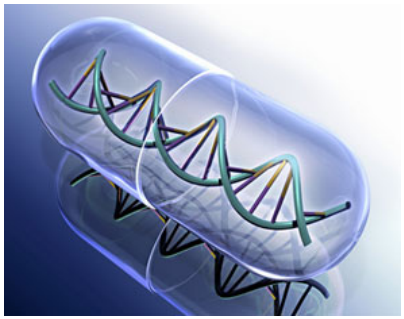
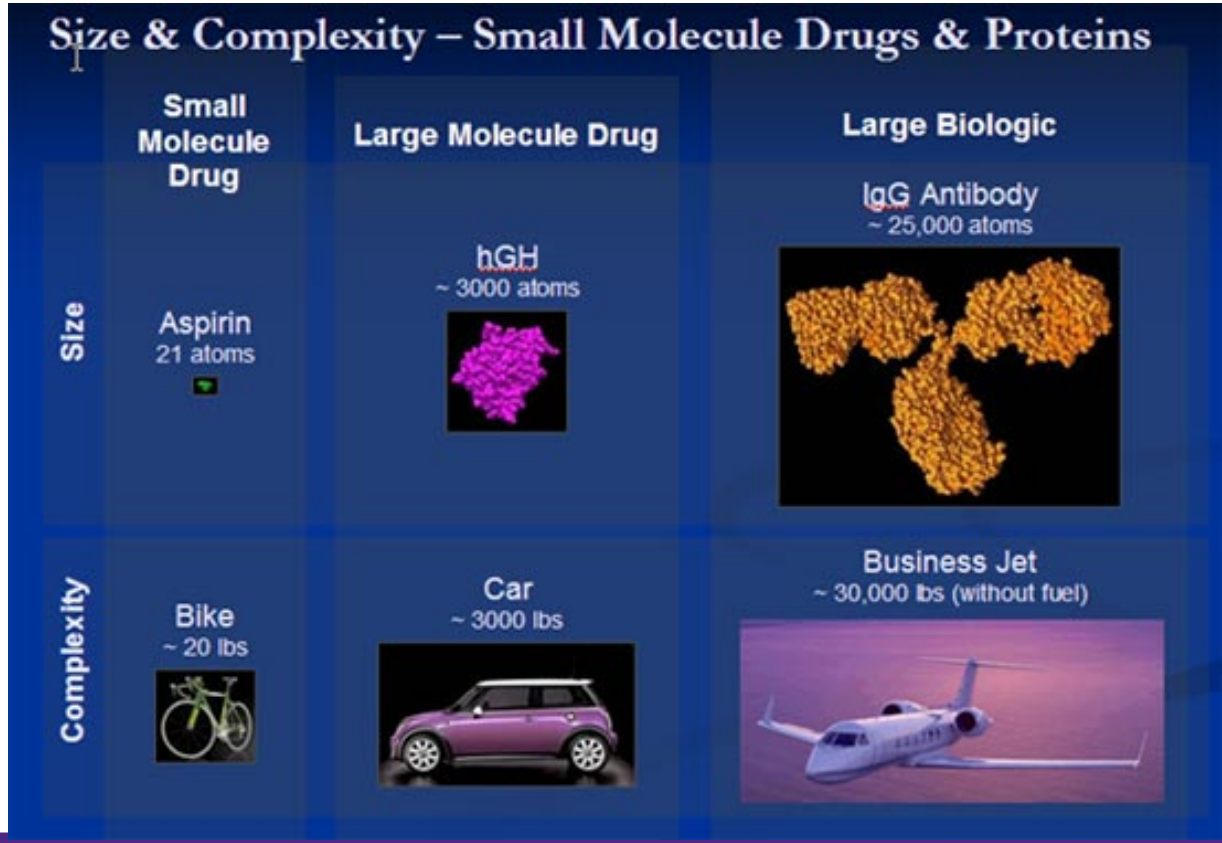
· CH3SO3H




Size & Complexity – Small Molecule Drugs & Proteins
Small Molecule Drug
Large Molecule Drug
Large Biologic
Size
Aspirin
21 atoms
hGH
~ 3000 atoms
IgG Antibody
~ 25,000 atoms
Complexity
Bike
~ 20 lbs
Car
~ 3000 lbs
Business Jet
~ 30,000 lbs (without fuel)

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