

Workshop on Post-Market Drug Safety and Effectiveness

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Professor and Director
McLaughlin Centre for
Population Health Risk Assessment

May 22-23, 2008

Noralou Roos

University of Manitoba

- Workshop objective: discuss use of postmarket drug safety and effectiveness (PMDSE) data in a:
 - Regulatory context
 - Drug plan management context
- Work towards development of a pan-Canadian pharmacovigilance network to fulfil the need for better PMDSE data to strengthen decision making practices



Steve Morgan

University of British Columbia

- Business case for proposed PV Network for Canada
 - Evidence gaps may cause harm
 - No single organization has mandate and capacity
 - Shortage of HQP
 - Need coordinated, timely studies
 - *Need high quality science*
- Centres of Excellence:
 - ADR reporting centres
 - Intra-ministry research (rapid data access)
 - Primary outcomes research (clinical trials)
 - Academic data centres (including training)
 - Canadian Institute for Health Information
- Peer review: CIHR?
- Identified data gaps and research priorities to guide activities of the network



Cindy Evans

Health Canada

- Over 20,000 therapeutic drug products approved for use in Canada today (also 42,000 natural health products and 81,000 medical devices)
- Post-market risk management: signal detection and assessment, leading to risk mitigation (with risks balanced against benefits)
- International actions and media attention can play a role in risk management
- Share information with EMEA and FDA
- Pharmacovigilance key source of information on drug safety
- External collaboration and sharing of data keys to success of postmarket surveillance



Karen Timmerman

Health Canada

- Progressing licensing included in Bill C-51 (now in second reading)
- Last major revisions to the Food and Drug Act were made in 1950s and 60s: does not address real world safety and effectiveness (RWSE)
- Key elements of progressing licensing:
 - Life-cycle approach
 - Evidence-based
 - Planning and accountability
- Bill provides authority for collection of new safety and efficacy data once a drug is on the market
- Bill C-51 provides enabling legislation for regulations that will address enhanced pharmacovigilance and post-market benefit-risk management



Ginette Tognet

Patented Medicines Prices Review Board

- PMPRB focuses on 1,200 patented medicines
- Mandate:
 - Regulatory - prices of patented medicines should not be excessive
 - Reporting – pharmaceutical trends and R&D spending by patentees
- Scientific review conducted for new patented medicines; price tests applied as a separate step within three broad categories of medicines
- Seven comparator countries: France, Germany, Italy, Sweden, Switzerland, U.K., U.S.



“MNE: maximum non-excessive (price)”



Mike Tierny

Canadian Agency for Drugs and Technologies in Health

- Common drug review (started 2003) provides a single review of clinical and economic evidence for (authorized) drugs, leading to formulary recommendations
- 18 participating drug plans make final listing decisions
- 100 recommendations have been made by CADTH to date, with about half recommended for listing (90% acceptance by drug plans)
- Safety, efficacy, and effectiveness of drugs compared to alternatives
- Rationale for recommendations in public domain (respecting confidential information when necessary)
- Need to define when and how to apply 'coverage with evidence development (CED)'



Brent Fraser

Ontario Ministry of Health and Long-term Care

- Clinical information provided for drug safety evaluation generally not directed towards reimbursement decisions
- Need to consider what types of clinical studies would be suitable for CED (e.g., place of therapy)
- Safety information limited by:
 - Small numbers of patients
 - Exclusion of high risk patients
 - Lack of adequate post-market data
- Need to consider implications of progressive licensing for reimbursement policy
- Need to refine information needs for listing agreements, including roles of clinical and observational data
- Drug innovation fund:
 - Drug access and innovation
 - Optimal use of drugs
 - Drug adherence



Susan Pierce

Health Canada

- Federal health plans include:
 - Non-insured Health Benefits (NIHB)
 - Veterans Affairs Canada (VAC)
 - Other groups
- NIHB provides 100% coverage to First Nations and Inuit (as a 'payer of last resort')
- NIHB has young client base, with higher than average disease burden
- Cost pressures due to increasing population, utilization, and costs
- Adhere to principles of CDR (evidence based and cost-effective)



Neena Chappell

University of Victoria

- Cholinesterase inhibitors not covered in British Columbia, because of limited RCT evidence of clinical effectiveness
- Alzheimer's Society and geriatricians encouraged 3 year trial to evaluate these drugs
- Five projects initiated:
 - Cost and utilization
 - Clinical epidemiology
 - RCT
 - CLIMAT (clinical assessment of dementia)
 - Caregiver appraisal
- Objective: provide sufficient information to Pharmacare to rewrite provincial eligibility for coverage
- Estimated cost of \$78 million (most of which is the costs of the drugs)



Judy McPhee

Nova Scotia Department of Health

- Cancer drug costs increasing 25-30% annually in recent years
- Cancer Systemic Therapy Policy Committee (CSTPC) formed in Nova Scotia to assist in allocation of limited funding
- Drugs typically afford small treatment benefit, lack robust clinical data and economic data
- Intense public pressure to fund: need decision making framework with broad input



Jeff Kirby

Dalhousie University

- Decisions involve evidence, economics, and ethics
- Broad multi-stakeholder group (CSTPC)
- Establish values and principles to guide decision making: beneficence, health equity, efficiency, sustainability, justice
- Recommendation options identified and evaluated
- Ethics facilitated dialogue included as part of process
- Recommendations made to Deputy Minister (minority opinions may also be presented)



Muhammad Mamdani

St. Michael's Hospital

- Multiple sources of drug-related research: expert opinions, clinical trials, case reports and case series, clinical registries, systematic reviews and meta-analysis, secondary databases
- Establish hierarchies of evidence? (despite limitations, all sources are of some value)
- How should differences between RCT and RWSE data be interpreted?
- How should conflicting evidence be resolved? (e.g., clinical/cohort studies showing decreased and increased cardiovascular mortality following HRT use)
- How do we study what's happening in the real world? (intervention trials? cross-sectional time-series? case-control? case-crossover? other?)



Muhammad Mamdani (cont'd)

St. Michael's Hospital

- Key challenges:
 - Understanding data sources (local expertise)
 - Understanding and applying appropriate methodology
 - Creation of infrastructure and data access
 - Governance and operational models
 - Need high quality information in a timely manner
- Opportunities
 - Expertise available across Canada
 - Rich data resources
 - *Can build pan-Canadian pharmacovigilance network to meet real world drug safety and effectiveness needs*



Mary Wiktorowicz

Global Comparisons

- What are 'best practices' in pharmacosurveillance internationally?
- NZ's ADR reporting rate high because of inclusion in electronic health record
- Postmarketing studies contracted to National PV Centre at University of Otago
- Government sponsored datamining: UK General Practice Research Database (400 research articles published)
- U.S. National Electronic Injury Surveillance System – Cooperative Adverse Drug Event System (NEISS-CADES)
- US FDA Amendments Act (2007): new database with 25 million patient years of observation



Mary Wiktorowicz (cont'd)

Global Comparisons

- UK can request Phase IV studies as part of a risk management plan
- EMEA risk management plans (RMPs) and strategies can be a condition of market authorization
- National PV committee and 31 regional PV centres in France (observational studies), linked to drug regulator
- EMEA products subject to five year renewal (onus on regulator to show there is a problem)



Mary Wiktorowicz (cont'd)

Global Comparisons

- US, UK, France and NZ all have links between the regulator and research networks
- More than 60 centres in ENCEPP (European Network of Centres for Pharmacovigilance and Pharmacoepidemiology)
- In Italy, drug companies contribute 5% of promotional budgets to support postmarketing research



Mary Wiktorowicz (cont'd)

Global Comparisons

- Prescription reimbursement done at national level in most countries other than Canada and the U.S.
- National regulators and drug benefit plans are commissioning postmarket studies from PV research centres
- As Health Canada moves to progressive licensing, enhanced pharmacovigilance will become of increasing importance
- Canada well-positioned to realize the potential for a national network of research centers



Ralph Edwards

World Health Organization

- Adverse drug reactions often demonstrated in a minority of vulnerable people (often $< 1/1000$)
- Five essential activities:
 - Signal detection
 - Analysis of issues relating to the signal
 - Benefit risk analysis
 - Communication of results to health professionals and patients
 - Consequence evaluation



David Henry

Institute for Clinical and Evaluative Sciences

- Pharmacovigilance system in Australia relies heavily on voluntary ADR reports (useful for hypothesis generation)
- Spontaneous ADR reports have identified drug safety issues that have been acted upon (Lumiracoxib, 2007)
- Potential for record linkage/EHR still to be realized



David Blumenthal

Institute of Medicine Committee on Drug Safety

- Inadequate quantity and quality of post approval data, and inadequate ability to monitor drugs postmarket
- Need to carry the strengths of the preapproval process to the postapproval period
- Recommended lifecycle approach to drug risk and benefit analysis
- Improve communication with patients and the public
- Approval should not be the 'last call' for realistic and effective action on drug safety



Bob Peterson

University of British Columbia

- Two basic decisions:
 - Should a drug be permitted for sale in Canada?
 - Should a Public PharmaCare program pay for a drug product?
- Should evidence from CT's support both decisions? (ideally, yes, but this is not the case at present)
- At the time of completion of Phase 3 studies, we really do not know much about the drug
- Safety determined in clinical trials is redefined in the 'real world'



Bob Peterson (cont'd)

University of British Columbia

- How to resolve information gap for new drugs?
 - Case I: Keep current rules for approval, but require more development work by industry
 - Case II: Progressive licensing (re-reviews during product life-cycle)
 - Case III: New research environment for post-market evaluations (need national strategy and access to linked databases)



Robert Leitch & Fern Levine

Charge to Break Out Groups: **Regulatory Context**

- What is the best mix of safety and effectiveness data to strengthen drug regulatory decision making in practice?
- What is the value added of looking at risk within population subgroups?



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Robert Leitch & Fern Levine

Charge to Break Out Groups: **Drug Plan Management Context**

- What are the obstacles to using postmarket data on drug safety and effectiveness in drug plan management?
- How can these obstacles be overcome?



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Break Out Group Reports: Regulatory Context I

- Need mix of benefit and risk information:
 - Will need different methodologies for benefits and risk assessment
 - Align international approaches (when possible)
 - Need for openness and transparency
 - Mix may vary with severity of outcome
 - Standardized, consistent use of data
- Need information sharing pathways between researchers and decision makers



Break Out Group Reports: Regulatory Context II

- Examine subgroups at risk?
 - Children, small population cancers, personalized medicine, First Nations
- Benefit and risk assessment more challenging for subpopulations
 - May need specialized statistical methods for small samples (international collaboration to increase sample size)
- Electronic Health Record:
 - Ensure information collected will be able to answer scientific questions of concern
 - Network might identify information needs for EHR
- Off-label use may be addressed in specific subpopulations



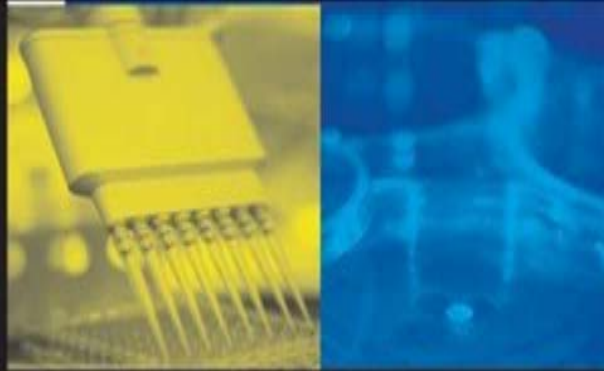
Break Out Group Reports: Drug Plan Management Context

- Openness
 - Is all of the information captured?
 - How can it be shared?
- Transparency in decision making
- Expertise:
 - Need right experts
 - Balance conflicts of interest
- How to respond to information?
 - May be policy constraints
- Balancing overall societal benefit
 - Managing expectations of different groups
- Overcome obstacles by:
 - Need for education (public, patients, politicians) and communication
 - Buy-in into decision making process
 - Use Infoway?
- Value of network:
 - Collectively discuss available evidence
 - Network with decision makers

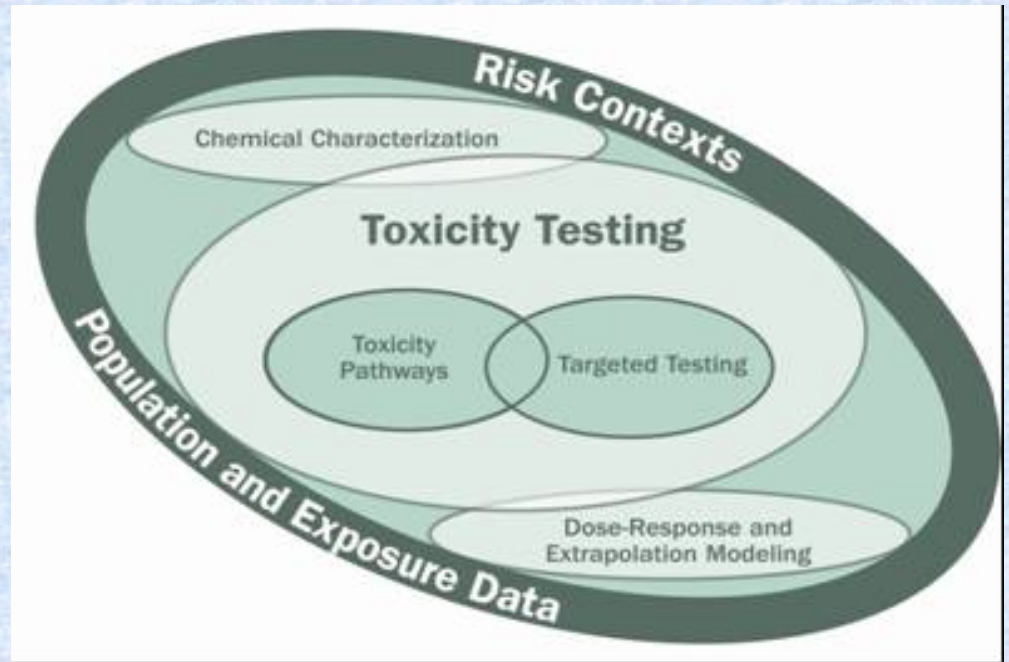




Related Developments: Toxicity Testing in the 21st Century



**TOXICITY TESTING IN THE 21ST
CENTURY: A VISION AND STRATEGY**



www.nas.edu

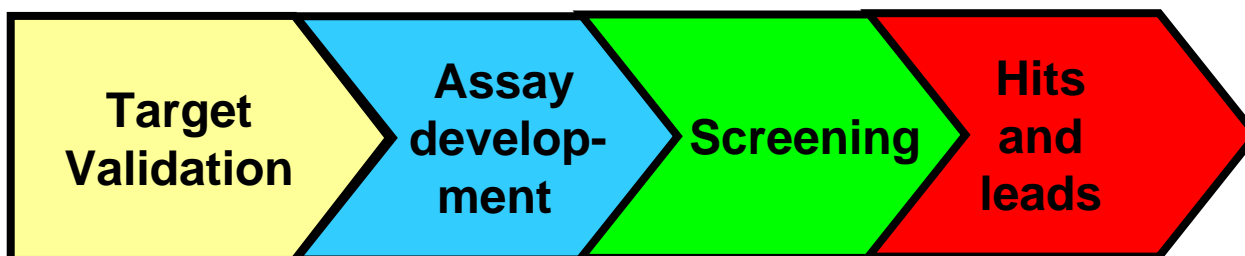
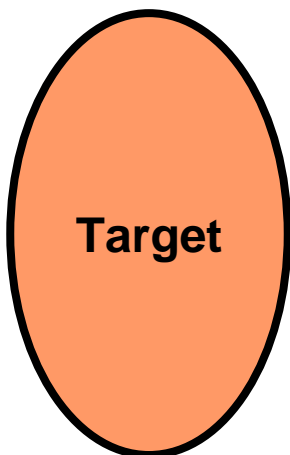
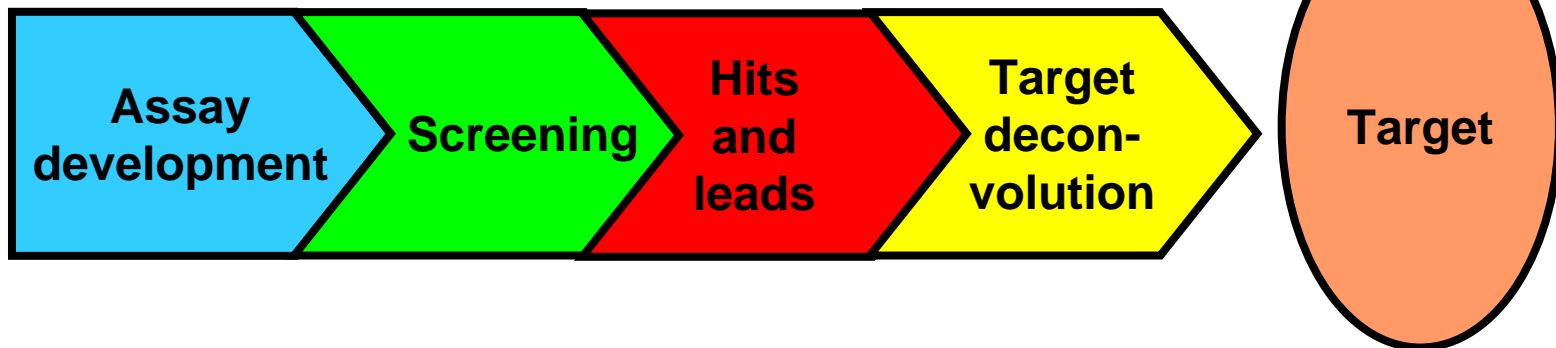
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Advisers to the Nation on Science, Engineering, and Medicine

Applications in the Pharmaceutical Industry?



Approaches to Drug Discovery

Phenotype-based



Target-based

[Adapted from: Terstappen, Schulpen, Raggiaschi & Gaviraghi (2007), Nature Reviews/Drug Discovery, 6, 891-903]

Next Steps

- Post presentations on web (CIHR/University of Ottawa)
- Workshop report
- Further development of the proposed Drug Safety and Effectiveness Network



Housekeeping Items

- **Workshop evaluations**
 - Leave outside meeting room
 - Fax: 613-562-5380
 - Email: dbedard@uottawa.ca
- **Name tags**
 - Leave outside meeting room



Thank You's: Steering Committee!

- **Madeline Boscoe, Canadian Women's Health Network**
- **Sheila Chapman, Canadian Institutes of Health Research**
- **Brent Fraser, Government of Ontario**
- **Jean Gray, Dalhousie University**
- **David Henry, Institute for Clinical and Evaluative Sciences**
- **Daniel Krewski, University of Ottawa**
- **Meghan McMahon, Canadian Institutes of Health Research**
- **Dale McMurchy, Canadian Institutes of Health Research**
- **Steve Morgan, University of British Columbia**
- **Bob Peterson, University of British Columbia**
- **Susanne Reid, Health Canada**
- **Noralou Roos, University of Manitoba**
- **Ingrid Sketris, Dalhousie University**
- **Cynthia Sundstrum, Dalhousie University**
- **Robyn Tamblyn, McGill University**
- **Mike Tierny, Canadian Agency for Drugs and Technologies in Health**
- **Mary Wiktorowicz, York University**



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Thank You's!

- Sponsor
 - Canadian Institutes of Health Research
- Organization
 - Daniel Bedard
 - Kate Burnett
- Speakers
- Facilitators
 - Fern Levine
 - Robert Leitch
- Participants



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Adjourned!



Levée de la séance!

