

Basis of Evidence for Critical Decisions in New Drug Marketing

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Two Basic Decisions

- Should a drug product be permitted to be ***sold*** in Canada?
 - Health Canada approval of CT's, Product Label, Safety Warnings, Dose and Dosage Forms, Manufacturing Standards
- Should a Public PharmaCare program ***pay*** for a drug product?
 - Is there value for cost? What are the opportunity costs? Does the use of the product drive other health costs?

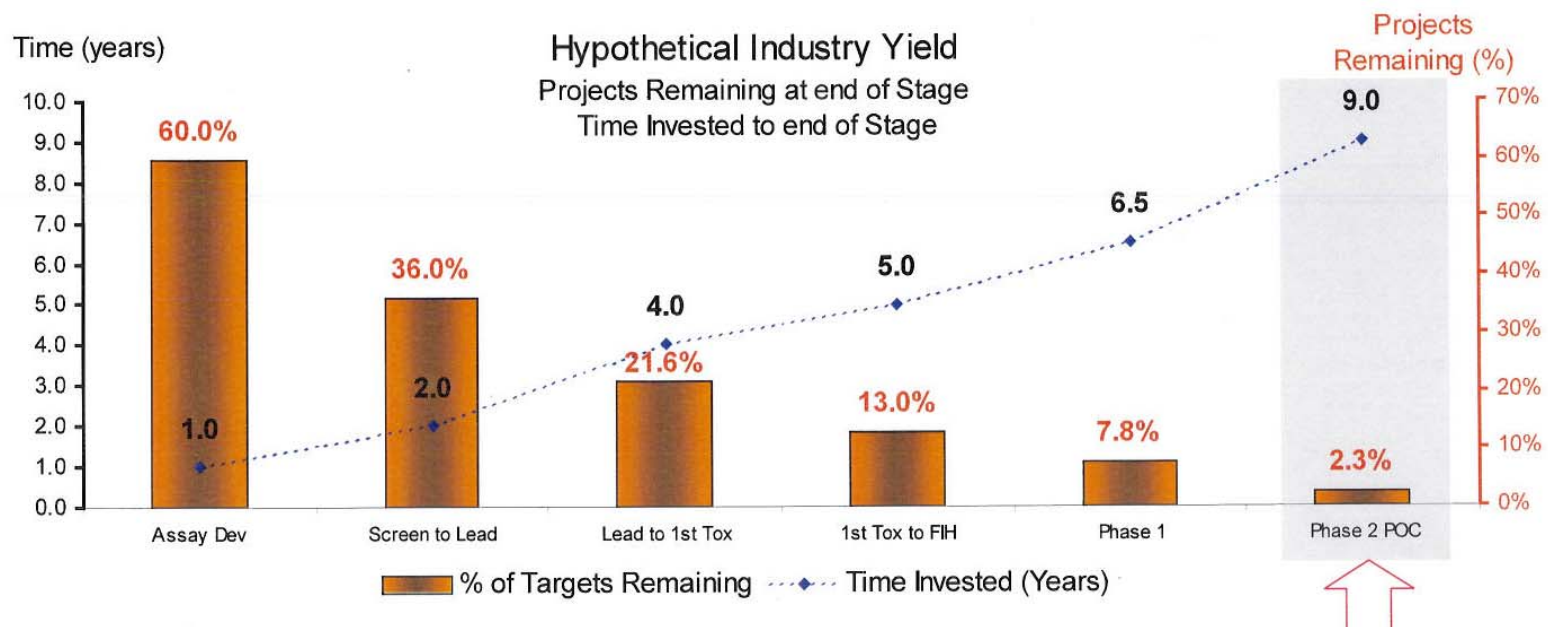
Should the evidence developed during CT's support both types of decision?

- In the ideal world (i.e, one without war, famine, taxes, etc) answer is: Yes
- In our current world, the type of evidence relied upon for each decision is submitted separately and is different.
- Much of the evidence developed around a new drug is intended to support a multitude of commercial decisions outside the regulatory or HTA environments.



The problem: survival to clinical POC...

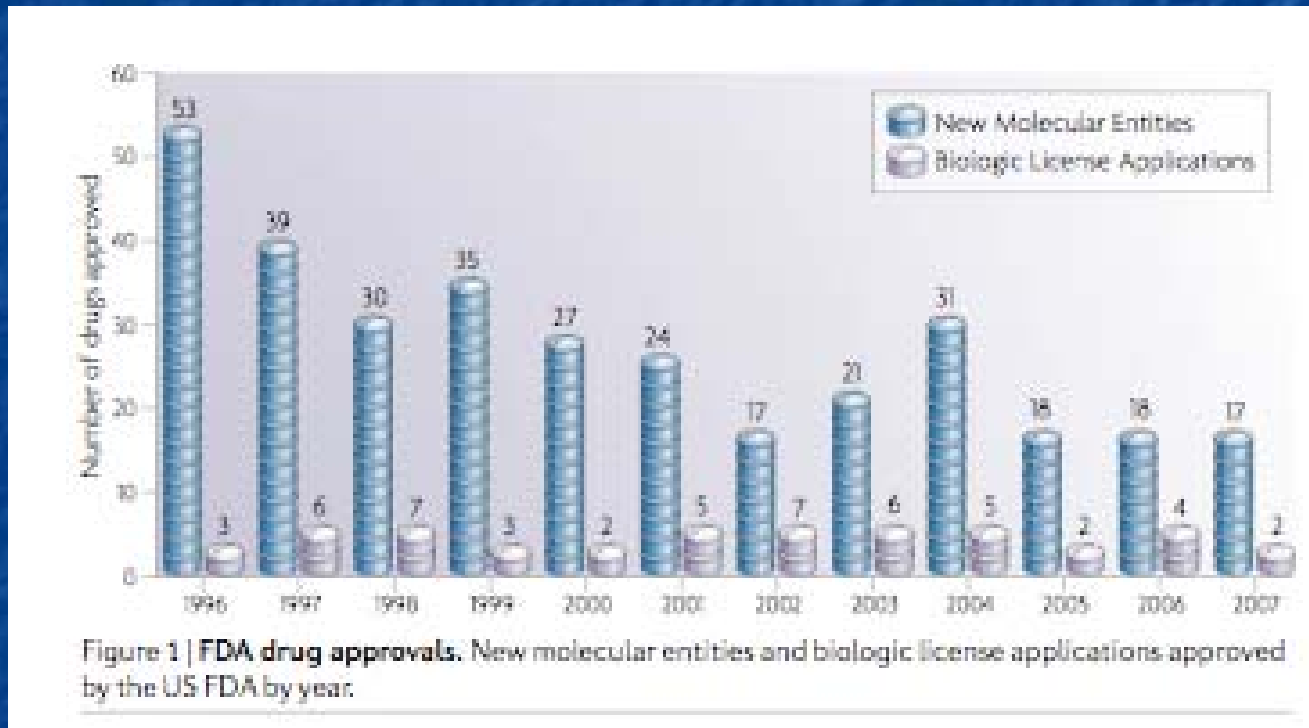
- 2% of Discovery projects will be successful to Commercial POC, and it will take 9 years to achieve successful POC.



Key Factors in Commercial Decisions

- There are many candidate medicines in the development pipeline
- Industry success rates in Phase 2 have fallen from 45% to 25% in the past 5 years (CMR Int'l survey data)
- Phase 2 studies can now take longer than Phase 3 studies
 - 2.8 years (1.5 years 5 years ago, *ibid.*)
 - Patient recruitment time for Phase 2 has doubled
 - Multiple sites often needed to complete Phase 2 studies
- Phase 3 study starts have fallen dramatically for industry
- New Chemical Entity market authorization applications have fallen
- Cost of drug development is linked to pricing
- Risk in developing new classes greater than taking the “me too” path
 - Consequently, many new “me too” market entries
 - Increasingly, same molecule, different enantiomer

Diminished NME Market Entries



POC Studies

- DB RCT, superiority against Placebo
 - Limits bias, provides assay sensitivity
 - satisfies statistical concern over random chance
- Short duration
 - Limits cost
 - Accommodates placebo arm
 - Compliant with requirement to get to market
- Early failures can lead to early kill decisions

Goals of Phase 2 Studies

- Proof of Concept
- Keep or Kill decision
 - driven by the necessity for a commercial success

Limitations of RCT's Leading to POC

- Can answer only one or a few questions per study
 - There are a multitude of questions surrounding new drugs
- Commercial sponsors of CT's are not primarily seeking to extend academic knowledge and produce publications
 - Seeking POC for efficacy, common safety issues, potential position in marketplace

Facts

- Phase 2 studies provide POC and allow commercial decisions to move to Phase 3
- Phase 3 studies are designed to extend POC and demonstrate reproducibility
- Phase 3 studies provide marginally additional safety information in a restricted population
- Experience during post market period frequently refines indications and safety information

Limitations of POC Studies

- Little information on long term use
- Little information on any but the most frequent safety issues
- Little information on drug interactions
- Little information in full target population for the marketed product
- Little information comparing to existing drugs
- Little information regarding appropriate utilization

Reality

- At the time of completion of Phase 3 studies, *we really do not know much about a new drug*
 - we have little predictive knowledge for how a new drug will behave in the “real world”
 - we have little knowledge for how a new drug will behave in any individual patient

Consequences of Current Drug Development Regime

- The information about the usefulness of a new drug is very limited.
- Outstanding questions at the time a new drug is marketed:
 - Where does the product fit in respect of other therapies?
 - What is the cost-effectiveness of the new drug?
 - How to introduce into sub-populations not studied in the qualifying CT's?
 - How to collect information on safety for less common and rare, but serious adverse events?

Why are Commercial Decisions Driving New Drug Development?

- Governments have relegated new drug development to the for-profit commercial sector.
- Governments do not require extensive knowledge of a new drug prior to its sales.
 - Often "safety" determined in clinical trials is redefined in the "real world"
- Governments are typically not interested in the price of new drugs during the approval process

Data Required for Health Technology Assessment

- Information about the usefulness of a new drug in the general population:
 - Where does the product fit in respect of other therapies?
 - How to introduce into sub-populations not studied in the qualifying CT's?
 - How to collect information on safety for less common and rare, but serious adverse events?
 - How to collect information on safety for commonly occurring medical events that may be attributable to the new drug? (e.g. M.I.)
 - What is the cost-effectiveness of the new drug?

Data Needed for HTA (con't)

- Information on long term use
- Information on any but the most frequent safety issues
- Information on drug interactions
- Information in full target population for the marketed product
- Information comparing to existing drugs
- Information regarding appropriate utilization

How to Resolve the Information Gap in Decision-making for New Drugs?

- Case 1: (Keep current rules for approval)
 - Require more drug development work by industry
 - Time to introduction to market will be longer
 - CT enrollments will need to be >10,000
 - Comparison drug trials will need to be done
 - Intellectual property time “on market” diminished
 - Costs of new drugs will definitely rise
 - Expect even more “me too” products
 - Will still anticipate surprises after full scale-up to real world

How to Resolve the Information Gap for New Drugs?

- Case 2: Progressive Licensing
 - Government now enters the drug development scene following POC by industry sponsor
 - Respects appropriate market entry times
 - Requires large safety studies
 - Allows appropriate controls on early utilization
 - Payers are involved
 - May require active comparator RCT's
 - Structures re-review of safety and efficacy data during product's life-cycle

How to Resolve the Information Gap for New Drugs?

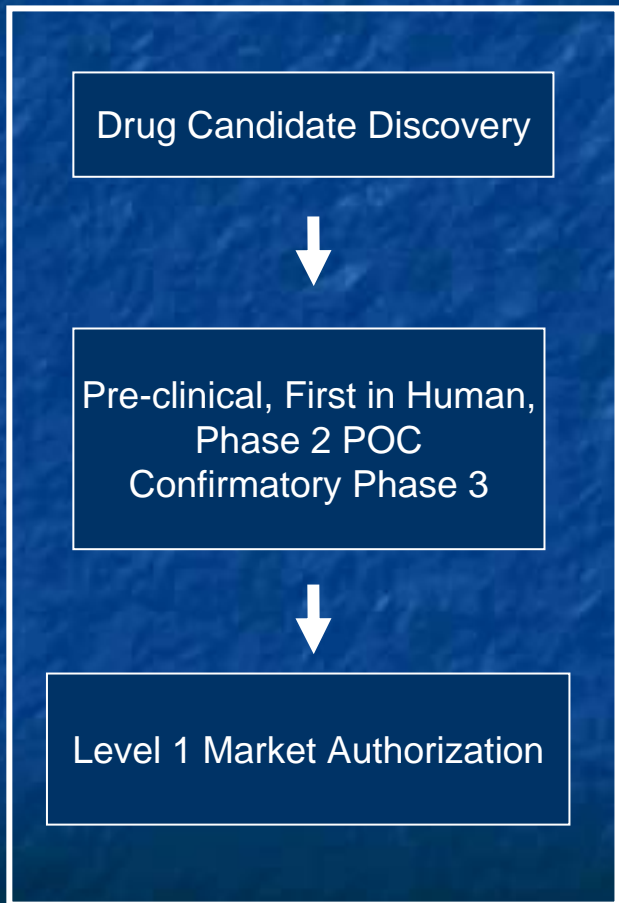
- Case 3: Create a New Research Environment for Structured Post-market Evaluations
 - Need a national strategy to develop new drug evidence beyond the purely commercial sector
 - Needs to be integrated with needs of “life-cycle” risk:benefit assessment by Health Canada (Bill C-51)
 - Needs to be responsive to HTA at payer level
 - Needs to be responsive to ongoing information needs of prescribers and consumers, i. e., needs to be in the public domain
 - New methods may be required to strengthen information derived from health services linked databases
 - Improved confidence from observational studies to add to evidence from RCT’s
 - Reduced cost of developing the new data
 - Remove haphazard approach to ADR reporting
 - Strengthen bare Proof-of-Concept data developed during pre-market CT’s

What is the Path Forward?

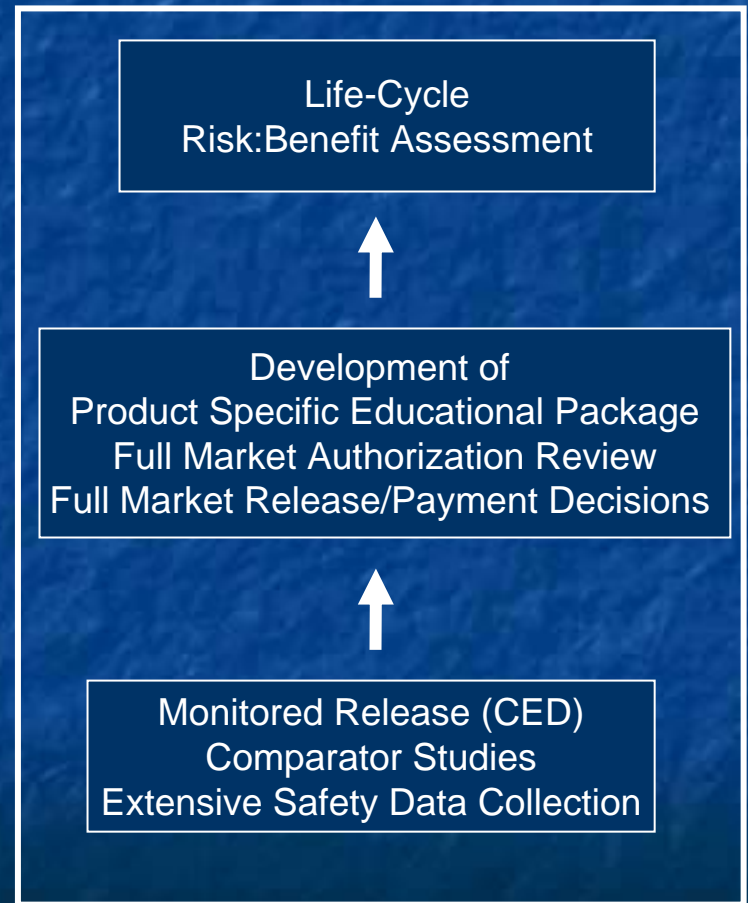
- Not Case 1
- Case 2 provides a structured approach, but is hugely demanding of new data which will be challenged by the pitfall of falling back into Case 1 if industry is responsible for producing all the data
- Case 3 is supportive of data generation, but lacks the decision-making role of Health Canada around labeling, etc
- Suggest both Case 2 and Case 3 are needed

How it might look:

Commercial Phase



Public Phase



In closing:

Present commercial and regulatory decisions are based upon RCT's which do not answer the multitude of questions surrounding a new drug.

We can provide a definitive answer to any question using a RCT, but other methods can work. This is particularly the case for safety studies.

Parachutes are effective

(but never proven in a placebo controlled RCT)

