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# Regulatory perspective on Biomarkers and Surrogate Endpoints

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May 6, 2012



Canada

# Overview

- ❖ Background
- ❖ Biomarkers and Surrogate endpoints
- ❖ Biomarkers: Regulatory considerations
- ❖ Conclusions



# Background

- ❖ Biomarkers are not a new concept
- ❖ In the past 8-10 years, largely thanks to the FDA's Critical Path Initiative, biomarkers have become the focus of regulatory activities, internationally
- ❖ The purpose of these activities was, and continues to be,
  - ❖ a better way to develop drugs,
  - ❖ to develop better (more effective/efficacious and safe) therapies
- ❖ Much activity has ensued: several Canadian research Institutions have joined some of the Biomarker networks established in the USA



# Background

- ❖ More recently, the CIHR and Genome Canada have also contributed to stimulating the science of biomarkers and there is active research ongoing in Canada in many institutions
  - ❖ These Institutions have initiated some public debate on the issues related to biomarker
- ❖ The results were activities around “personalised medicine” with a workshop that was held by Health Canada with the involvement of various stakeholders in January, 2012



# Background

- ❖ We are looking forward to where this will lead to in Canada
- ❖ The end result will most likely be some type of collaborative venture between the members of the health portfolio
  - ❖ The members of the portfolio include: MDB, BGTD, TPD as well as CIHR, PHAC, PMPRB...
- ❖ The integration of biomarkers into the regulatory environment is ongoing: there were some 40+ therapeutics labelled with information on biomarkers at the time the workshop took place
- ❖ It is likely that there are more now, many of which fall in the ambit of targeted therapies



# Biomarkers and Surrogate endpoints

- ❖ Neither Biomarkers nor Surrogate endpoints are entirely new
- ❖ Both had been used for some time both in medicine and drug development for therapeutic/medical decision-making as well as in the regulatory world and range from:
  - ❖ Simple measurements such as blood pressure, cholesterol levels, X-rays and some typical signs that had been described.
  - ❖ Other examples used were different metabolic pathways for drugs that can determine their safety and efficacy: what we call to-day Pharmacogenomics
- ❖ The same biomarkers had been also used to follow disease states



# Biomarkers and Surrogate endpoints

- ❖ Advances in Science are now focussing on a multiple types of biomarkers:
  - ❖ Humoral: Known for some time such as CEA and PAS
  - ❖ Tissue: EGFR, K-ras, Her-neu, VEGF (3 of these 4 are used to “target therapies” and to improve outcomes, or stratify patients)
  - ❖ Imaging biomarker: X-rays, CAT-Scans, MRIs, PET scans, multimodality imaging
  - ❖ Some imaging modalities that are able to reveal subcellular structures



# Biomarkers and Surrogate endpoints

- ❖ Biomarkers have been used in medical practice for long time, even if under “other names”...
- ❖ Surrogate endpoints are not new either
- ❖ Some specific genomic markers were also considered in many instances to forecast the safety profile of some drugs (metabolic pathway; alternate pathways)
- ❖ It took many years to “validate” the older markers via clinical trials and many years of use



# Biomarkers and Surrogate endpoints

- ❖ Biomarkers and Surrogates endpoints may be used, and are used interchangeably, in therapeutic development and decision-making
- ❖ Biomarkers and Surrogate endpoints have also been used in drug development in the same way as they have been used in medical practice
- ❖ The area is, thus, not entirely new: In this presentation they are used as Biomarkers only



# Biomarkers: Regulatory considerations

- ❖ Canadian Regulations date from the 60's: we have no direct authorities currently
- ❖ Most activities we engage in, interpret those regulations (to some extent under the clause:..."information satisfactory to the Minister....
- ❖ Current regime does not have a firm definition of biomarker: there are pros and cons
- ❖ We apply the definition mainly to Genomics and targeted therapies
- ❖ Canadian Guidelines for Pharmacogenomics is not explicit on the biomarker issue but encourages submission of genomic data (allows for the submission of trials where biomarkers are used to define drug development and CT outcomes)



# Biomarkers: Regulatory Considerations

- ❖ No formal biomarker qualification programme in Canada
- ❖ No specific definition or qualification programme for Biomarkers or the specific validation of surrogate endpoints
- ❖ However, all data must be relevant to a particular product-related submission
- ❖ The simultaneous submission of diagnostics and therapeutics that are linked by a biomarker are strongly encouraged (e.g. Herceptin as the prototype for modern biomarkers; there are others as well)
- ❖ HC has been active and has been participating in all international activities on Biomarkers at various levels:
  - ❖ CIOMS
  - ❖ ICH: with E-15 and E-16: both adopted



# Biomarkers: Regulatory Considerations

- ❖ The FDA and the EMA are more advanced than regulators in Canada in biomarker qualification
- ❖ The approach is still case by case, but based in science and the applicability of the findings
- ❖ Canada has adopted both ICH Guidelines
  - ❖ ICH E-15 that deals with definitions and the coding of PGx data
  - ❖ ICH E-16 that also recognizes that, while the guidance refers mainly to genomic biomarkers, a biomarker is a biomarker, regardless its type or how generated
- ❖ Approach is to qualify a biomarker as “fit for purpose” and validate it analytically, primarily used a “safety biomarkers” to-date
- ❖ There is a need to validate clinically, that is to demonstrate the utility of the biomarker



# Biomarkers: Regulatory Considerations

- ❖ List of qualified biomarkers is posted on the FDA website
- ❖ EMEA participates in discussions on the qualification of biomarkers
- ❖ The HC-EMEA and the HC-FDA MOUs facilitate these discussions
- ❖ FDA encourages the simultaneous filing of submissions and diagnostics as “combination products”
- ❖ HC has encouraged and continues to encourage the development of therapeutics with biomarkers
- ❖ HC’s guideline differentiates on how they are used



# Biomarkers: Regulatory Considerations

- ❖ In Canada, the MDB validates analytical methodology; does not qualify nor determine the clinical utility of the biomarkers
- ❖ The qualification and clinical utility are left up to TPD and BGTD
- ❖ Industry files submissions without necessarily linking biomarkers to outcomes, safety or efficacy/effectiveness



# Biomarkers: Regulatory Considerations

- ❖ The regulator is left to consider whether and how to adopt a biomarker for decision-making when a submission is reviewed
- ❖ Interactions with researchers will help HC move the field forward
- ❖ Regulatory modernization and life-cycle management of therapeutics are uniquely suited to allow scientific innovation to reach the regulatory field
- ❖ Should Canada adopt the FDA's biomarker list?



# Biomarkers: Regulatory Considerations

- ❖ Biomarkers vary with several factors including the disease entity
- ❖ Biomarkers as surrogate endpoints are of a varied nature: reflect disease process or the pharmacologic response to a therapeutic agent or safety or effectiveness of the product (drug, biologic, device, etc.)
- ❖ Biomarkers can be used as surrogate endpoints, but need validation in clinical trials of sufficient size to allow statistical validation, or with designs suitable for the purpose may be small in size
- ❖ Biomarkers part of medical practice: therefore used in clinical trials and submissions for marketing as a means of defining the efficacy of a therapy



# Biomarkers: Regulatory Considerations

- ❖ Important to recognise and determine which rated parameters of disease would qualify as surrogates in the regulatory setting
  - ❖ e.g. Cholesterol (HDL/LDL levels); ER/PR Status; CEA in Ovarian Cancer; PAS for prostate cancer; Her/neu; K-ras; respiratory assistance in Hurler's syndrome; development of antibodies as evidence for immunity with Vaccines
- ❖ Progress in science and medicine have forced the consideration of end-points that make sense, long before clinical benefit (that is long-term benefit) can be proven
- ❖ Have the potential and purpose to shorten drug development



# Biomarkers: Regulatory Considerations

## Additional examples

- ❖ Enzyme replacement product for genetic diseases
- ❖ Drug products used to treat a variety of diseases:
  - ❖ Cardiovascular Diseases and/or their symptoms; Diabetes; Cancer; GI Diseases (Crohn's Disease; Ulcerative Colitis, etc.)
- ❖ Ideally, clinical benefit is preferred; however, current regulatory approaches allow to collect additional information following market authorisation



# Biomarkers: regulatory considerations

## Additional considerations:

- ❖ The question remains how they relate to long-term clinical benefits, one of the objectives of the regulatory process
- ❖ The use of biomarkers followed by clinical validation underscores the iterative and dynamic nature of drug development
- ❖ Regulatory process likes certainty: without that certainty, labels for products can not be constructed well
- ❖ There is a need to determine how the regulatory system can define better the value of Biomarkers and Surrogates?
- ❖ Our health care system also likes certainty when making decision on reimbursement of treatments



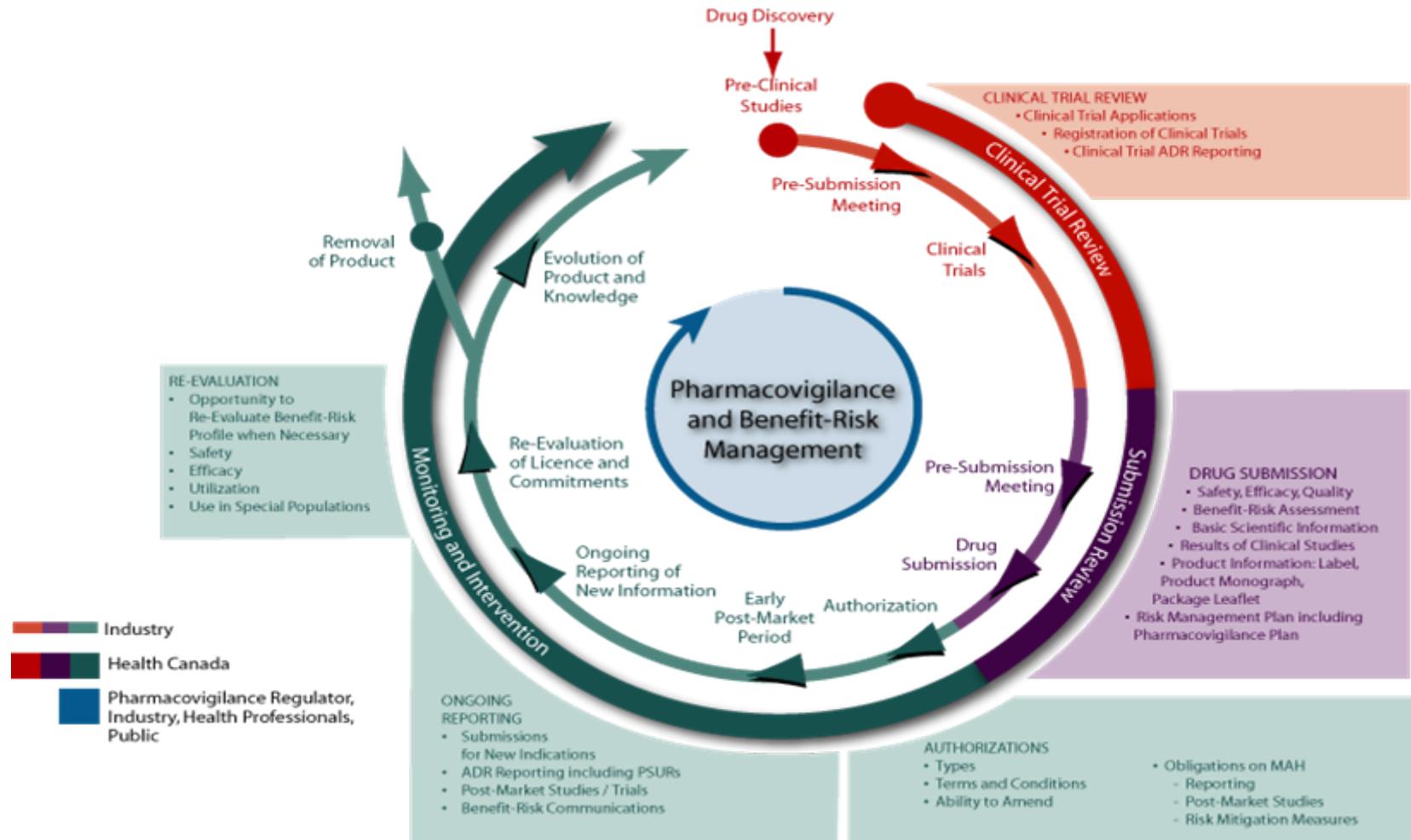
# Conclusions

A multiplicity of elements need to be considered in utilising biomarkers in drug development:

- ❖ Building on medical uses
- ❖ Needs for concomitant development of testing (in-vitro devices: class III devices)
- ❖ Analytical and Clinical Validation of Biomarkers (clinical utility)
- ❖ Use of biomarkers as opposed to clinical benefit as endpoints
- ❖ Labelling, prescribing, incorporation into common use
- ❖ Differing views of the regulatory system, pricing system and health care system
- ❖ Education of physicians, other health care professionals and the public



## Progressive Licensing Model



# Thank you

# Questions ?

