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Regulatory perspective on Biomarkers and Surrogate Endpoints

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Canada

Overview

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

Background

- Biomarkers are not new (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 biomarker and there is active research ongoing in Canada in many institutions
- This has translated into activities around “personalised medicine” with a workshop that was held in January, 2012
- We are looking forward to where this will be going as a collaborative venture between the health portfolio members
- The integration of biomarkers into the regulatory environment is ongoing: there are some 40+ therapeutics labelled with information on biomarkers

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
  - Examples were as simple as measurements of blood pressure, cholesterol levels, signs described on X-ray
  - Other examples used were different metabolic pathways for drugs that can determine their safety and efficacy: what we call to-day Pharmacogenomics
  - Also used to follow disease states

Biomarkers and Surrogate endpoints

- Advances in Science are now focussing on a multiple types of biomarkers:
  - Humoral: CEA, PAS, etc
  - Tissue: EGFR, VEGF, K-ras, Her-neu
  - Imaging biomarker: from Xrays to multimodality imaging markers
  - New and developing modalities that can image cellular structures to subcellular structures

Biomarkers and Surrogate endpoints

- Biomarkers have been used in medical practice for long time, even under “other names”…
- Surrogate endpoints are not new either
- Biomarkers and Surrogates endpoints may be, 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

- Regulations date from the 60's: no direct authorities
- Most activities interpret those regulations
- Current regime does not have a firm definition of biomarker: pros and cons
- Definition mainly applied 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)
- HC has been active and has been participating in all international activities on Biomarkers (and Surrogate Enpoints) at various levels:
  - CIOMS
  - ICH: with E-15 and E-16: both adopted

Biomarkers: Regulatory Considerations

- The USA and the EMA have a formalized the regulatory approached to the biomarkers qualification process
- These consist of “biomarker qualification submissions”, as part of a self-standing submission or part of a drug submission
  - ICH E-16 allows for both eventualities
  - ICH E-16 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 (e.g. 7 renal biomarkers posted by the FDA)
- 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

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 products 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:

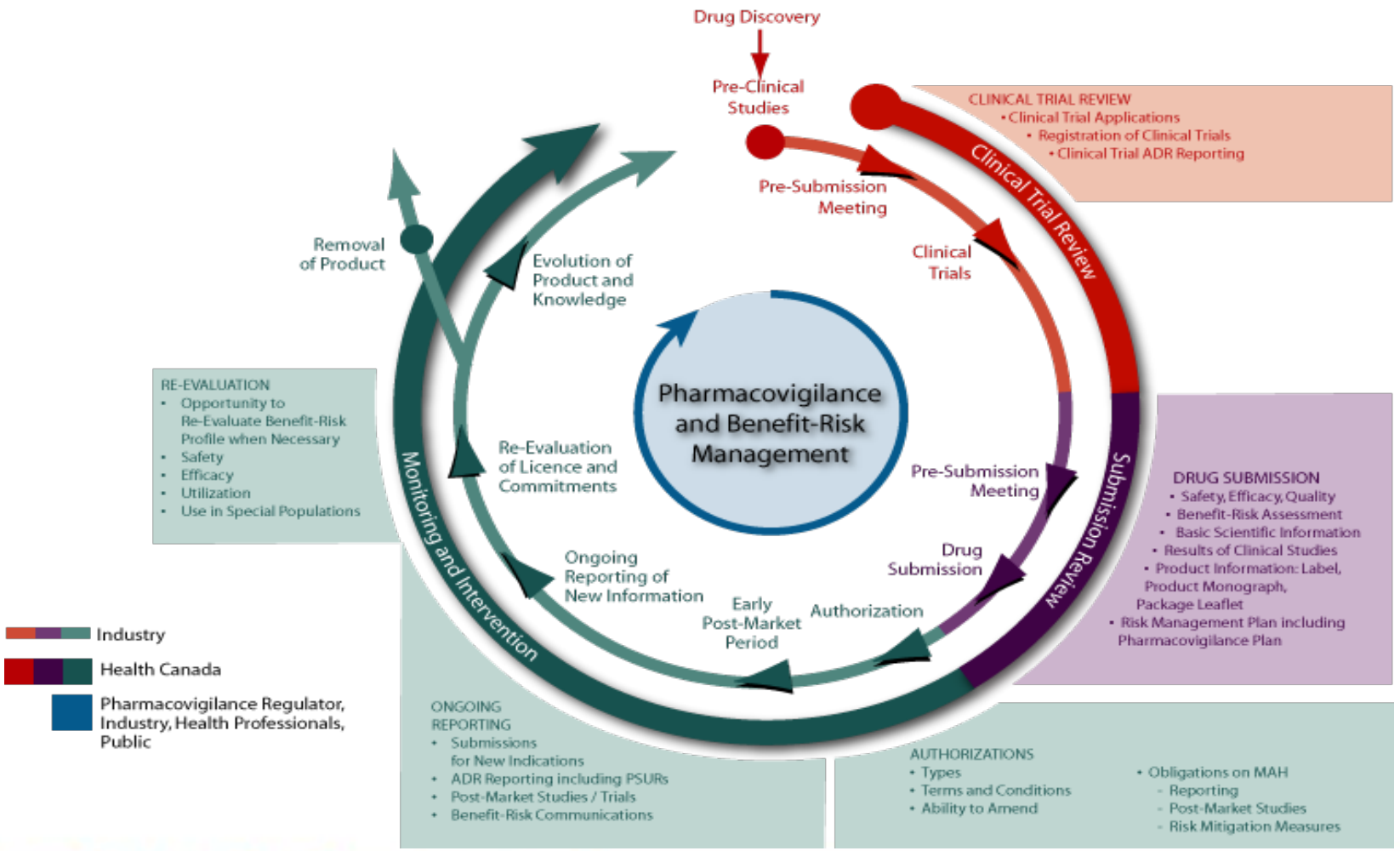
- The question remains how they relate to long-term clinical benefits, one of the objectives of the regulatory process
- The use of biomarkers followed by clinical validation underscores the iterative and dynamic nature of drug development
- Regulatory process likes certainty: without that certainty, 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 ?