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Rewards and Risks of using Surrogate Endpoints in the Approval of Drugs

Agnes V. Klein, MD

Biologics and Genetic Therapies Directorate

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Points to Consider

- Regulatory Definitions/Considerations
- Biomarkers as Surrogate Endpoints
- Market authorization based on surrogate markers vs clinical benefit
- Specific examples
- Issues for consideration
- Conclusion



Regulatory Definitions/ Considerations (1)

- There are no regulatory definitions for “Surrogate Endpoint”, in Canada
- There is, however, a common understanding and recognition of what is meant by the term, based on the most commonly accepted definitions from the literature
- Definitions from other regulators are also considered, as well as the definition utilized by the centralized formulary assessment organization in Canada (CADTH and CDR)
- Generally, the definition is used in the context of clinical trials that are used in support of the market authorization for new products



Regulatory Definitions/ Considerations (2)

- Surrogates are varied
 - Biomarkers reflecting a physiologic or pathologic process
 - Surrogates that reflect the usual course of disease: for example such as the surrogate that was used recently in the development of a new product for Heart Failure
 - Other surrogates:
 - HbA1c as a surrogate for level of diabetes control
 - Physiological and function measurements in some genetic diseases (Elaprase)
 - Disease Progression or Remission as surrogates in the treatment of Cancer



Regulatory Definitions/ Considerations (3)

- There is a clear understanding and recognition that surrogates vary with the disease entity
- There is also a recognition that surrogate endpoints are of a varied nature, reflecting the disease process or the pharmacologic response to a therapeutic agent (drug, biologic, device, etc.)
- There is also a recognition that biomarkers can be used as surrogate endpoints, but that they need validation in clinical trials of sufficient size to define statistical validation
- Alternately, if the trial is small, the design has to be suitable to validate the biomarker as surrogate
- Consultation with the regulator is advisable



Biomarkers as Surrogate Endpoints

- Biomarkers form part of medical practice: therefore are used in clinical trials and submissions for marketing as a means of defining the efficacy of a therapy
- The question is 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 usually are non-committal
- In Canada, the health care system also likes certainty when making decision on reimbursement of treatments



Biomarkers as Surrogate Endpoints

- We consider it important to recognise and determine which rated parameters of disease would qualify as surrogates in the regulatory setting
 - Examples used: Cholesterol (HDL/LDL levels); ER/PR Status; CEA in Ovarian Cancer as reflection of disease activity; 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
- There is a need to determine how the regulatory system can define better the value of Surrogates?



Market authorisations based on Surrogate Endpoints vs clinical benefit

- Enzyme replacement products for genetic diseases
- Some drug products used to treat Cardiovascular Diseases and/or their symptoms
- Treatment of Diabetes
- Therapeutics for the treatment of Cancer
- Some 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



Specific examples: Products to treat Cancer

- In general, our Oncologic Drugs Division uses Surrogates similar to those used by the FDA
 - Endpoints for “regular approval”, include
 - Response with or without tumour-specific symptoms
 - Response with time to progression
 - Response alone
 - Reasonably likely surrogates are also accepted
 - When there is lack of certainty but a “safety profile” is defined with preliminary evidence of efficacy: NOC/c
- Because practice of medicine, at least Oncology, are analogous in Canada and the US, and because most studies are multicentre and/or multinational, Canada accepts the approached taken for the US and based on their guidance



Issues for Consideration (1)

- Stem from the existence of a public system: CADTH and Common Drug Review (CDR)
- Regulatory decisions are questioned by CDR, especially the validation of Surrogate Endpoints
- At times, validation is hindered by studies being too small for solid statistical validation
- Surrogate markers may have different validity depending on the particular disease considered: eg for breast cancer adjuvant therapy, DFS is a valid surrogate for OS but not for all products
- The intent of the therapy, curative or palliative is important



Issues for Consideration (2)

- Surrogate endpoints may be considered more or less “valid” depending on the stage of the disease
- Ideally, validated, consistent, disease, disease stage specific surrogates are needed
- Should be accompanied by considerations and explanations on how these will translate into survival data
- Do considerations differ between different diseases?
- How to factor biomarkers and/or other measurements into this?



Conclusions

- Surrogate markers offer much promise from our perspective to shorten drug development
- New approaches to regulations also allow for such shortened development as these approaches include integration between pre-market and post-market activities in continuous and seamless regulatory activities
- The new regulatory framework in Canada, under the name of Progressive Licensing Framework was structured with just such integration in mind
- The framework also allows unconventional paths for the development of products to shorten time to market and would include post-market validation studies amongst other activities

