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Commentary Article

Biomarkers in Health Product Development: Commentary

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Introduction

As defined in a previous case report by Archambault and Plourde (2017), a biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention based on scientific evidence [1]. Archambault and Plourde (2017), using supporting example from patient with advanced prostate cancer has indicated that biomarkers should be considered as a tool to improve the development of health product [1]. The biomarker should be reproducible within patients; responsive to clinically meaningful changes in disease activity; change in expected direction with known effective treatments and; that the biomarker of interest should be related to the causal pathway of the disease [1-2].

The scientific background of biomarkers involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or the measurements of specific indicators such as blood pressure or radiographic images, serum or plasma) in relation to clinical endpoints of interest [1-2]. Obviously, biomarker research can play an important role in all phases of health product development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies i.e., throughout the life-cycle of a health product discussed in the review by Maher M et al [3]. The clinical research with biomarkers is closely related to personalized medicine: which involves selecting the management strategies that are most effective for a given patient at a certain point in time [1-2,4]. The complexity of the treatment response in a patient and substantial variability across patients suggest that biomarkers may be more helpful in combination than alone. The identification of biomarkers that predict the treatment response prior to drug exposure is a priority in health product development [1].

An important goal of biomarker research is to help health care providers and the patients in the decision-making toward safer and more efficacious courses of treatment, in order to improve patient outcomes, and to reduce the overall cost for the patients and the health care system [1-2]. It also permits for the continued development of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population. A very good example of this is the Her2/neu over expression analysis required for prescribing trastuzumab (Herceptin) to breast cancer patients [5].

Many biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or specific events cannot practically or ethically be measured [4]. For instance elevated cholesterol levels increase the likelihood for heart disease and it is easier to measure cholesterol that waiting for the appearance of morbidity or mortality from heart disease.Which means that cholesterol acts as a surrogate for heart disease? [6].

As discussed in the case report by Archambault and Plourde (2017), by using biomarkers to assess patient response to treatment, ineffective health products or treatments may be terminated earlier in favour of more promising health product [1]. For instance in this case report, it was decided that Casodex should be eliminated in favour of a better treatment with Zytiga because the treatment with Casodex has demonstrated a high PSA doubling time, suggesting that this product was becoming less efficient [7-8].

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Health authorities and researchers are increasingly aware of the benefits of biomarkers and how they may be used for health product development and approval, clinical trial design, and clinical care. For instance, health authorities such as the FDA (USA), EMA (European Union), MHLW (Japan), and ICH (International Conference on Harmonisation) are playing a key role in advancing this scientific field by creating the regulatory infrastructure to facilitate its health product development [4,9].These health authorities encourage the integration of biomarkers in drug development and their appropriate use in clinical practice. They believed that this approach will help promote innovation in the development of new medical products, and, ultimately, lead to a more personalized medicine. Accordingly, interesting documents on this issue are obviously the ICH Guidance's E15 and E16 (4,9). In these documents, regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this area [2,4,9]. It is not the purpose of this commentary to discuss all the elements to consider for the appropriate use of biomarkers in health product development but mainly to generate discussion among scientist, regulatory agencies, universities, industry around this issue.

Biomarkers Used in Clinical Practice and Research

Biomarkers are already being used in clinical practice and clinical research for different reasons as follows (2):

To Predict Efficacy

The predictive efficacy of biomarkers can be used to determine which patients are most likely to respond to a particular health product(personalised medicine). Examples included: 1) Her2/neu over expression analysis required for prescribing trastuzumab (Herceptin) to breast cancer patients (5), 2) c-kit expression analysis prior to prescribing imatinib mesylate (Gleevec) to gastrointestinal stromal tumor patients (10), and iii) KRAS mutational status testing prior to prescribing panitumumab (Vectibix) or cetuximab (Erbitux) to metastatic colorectal cancer patients [11-12] are among these examples (2).

To Predict Safety

The predictive safety of biomarkers is used to select the proper health product and to evaluate the appropriateness of continued therapy in the event of a safety concern [2]. Examples include: 1) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin) together with daily long-term drug regimens that may increase serum potassium (13), and 2) prospective HLA-B*5701 screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen) (14). Zytiga a second-line hormone therapy in the treatment of advanced prostate cancer but this drug is known to be hepatotoxic [8]. It is unethical to wait for evidence of liver damage instead of evaluating morbidity and mortality; we can decide to reduce the dose; or to discontinue the medication on the basis of high liver enzymes elevations [8]. These examples reflect that biomarkers can be used to make the appropriate clinical practice decision faster and safer.

As Surrogate Biomarkers

Surrogate biomarkers may be used as alternatives to measures overall survival (OS) or progression free survival (PFS), metastatic free survival (MFS) for example (6). Surrogate biomarkers are measures that are based on epidemiologic, therapeutic and pathophysiologic evidences, or other evidence that predicts clinical benefit (2, 6). Examples include: 1) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor) (15), 2) blood glucose or glycated haemoglobin as a surrogate for clinical outcomes in patients taking anti-diabetic agents (6), and 3) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and OS in patients receiving antiretroviral therapy for HIV infection (6).

Prognostic Biomarkers

Biomarkers can also help predict clinical outcomes independent of any treatment modality (1-2). Examples of prognostic biomarkers used in clinical practice include: 1) Cell Search to predict PFS in patients with metastatic breast, prostate or colorectal cancer(16), 2)Anti-cyclic citrullinated peptide (anti-CCP) antibody testing is particularly useful in the diagnosis of rheumatoid arthritis, with high specificity. This biomarker presents early in the disease process, and increase the ability to identify patients who are likely to have severe disease and irreversible damage (17), 3) estrogen and progesterone receptor status for breast cancer (18), 4) antidsDNA for the severity of systemic lupus erythematosus [19] and PSA doubling time for the evolution of an advanced prostate cancer (1)are some examples of prognostic biomarkers.

Points to Consider for the Use of Biomarkers in Clinical Research

In the context of this commentary, it is not possible to discuss all possible regulation associated with the use of biomarkers in clinical research and clinical practice, but I will discuss some elements that we need to consider in order to give to the readers a quick overview on the legal aspects associated with the use of biomarkers in health product development. For more information the readers is invited to consult the ICH E-15 and ICH-E16 guidance's [4,9] that describes the recommendations regarding context, structure and format of regulatory submissions for qualification as biomarkers [9].

Adequate Sample Collection and High-Quality Data

Obviously to collect adequate sample that will ensure high quality data, scientists should follow the recommendations from the ICH on Good Clinical Practice (GCP), on Good Manufacturing Practice (GMP) and on Good Laboratory Practice [20-22]. Clinical drug development programs are an invaluable resource and a unique opportunity for highly productive biomarker research. Pharmaceutical industries and university research centers are increasingly contributing to the consortium efforts by pooling samples, data, and expertise to maximize the probability of success in the identification of clinically relevant biomarkers [2,23]. As for other clinical trials in humans, research with biomarkers should ensure that:1) the research is scientifically sound; 2) the participants are informed of the scope of the intended research; 3) the autonomy is respected; 4) the standards for confidentiality protection respect as recommended by the ICH E6 guidelines on Good Clinical Practice [20] and by the Food and Drug Regulations for research performed in Canada [24].

Necessitate Voluntary Informed Consent

In accordance with the ICH E6 Guidelines on Good Clinical Practice [20], the collection of biological samples in clinical trials must be undertaken with a voluntary signed informed consent from the participant or from the patient's legally-acceptable representative. As for other clinical trials in humans the investigators should respect the recommendations from the ICH E6 Guidelines on Good Clinical Practice and the Canada Food and Drug Regulations [20,24] regarding the consent form for clinical trials performed in Canada. In other countries, policies and regulations for legally-appropriate informed consent may vary on national, state, and on local levels, but the informed consent are generally based on internationally recognized pillars of ethical conduct for research on human subjects that include respect for person, beneficence and justice [2, 23-26]

Withdrawal of Consent / Sample Destruction

The informed consent form should inform participants of their right to withdraw their consent or to request the destruction of their samples [20,24]. However, participants should be informed that it is not possible to destroy samples that have been anonymized as data already generated prior to consent for withdrawal request has been signed [27-29]. These data are to be maintained as part of the study data. To know more about the regulation surrounding the retention of data, please consult the following documents [27-29]. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research [2,27-29]. The processes for collection, labelling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected [4,9].

Privacy Risks and Patient Rights

Research organisms including universities, pharmaceutical industry and the regulators have developed policies and procedures for confidentiality protection to ensure that all data generated by clinical trials stay confidential [27-29]. Maintaining the privacy of study participants and the confidentiality of information relating to them is of great concern to industry researchers, regulators, and patients [20]. The ICH E6 has set standards that provide assurance that the data and results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected. This standard dictates that "the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements [20]. In addition, research data should not be included as part of a participant's medical record accessible for use by insurance companies, for example (2).

Conclusion

The use of biomarkers has the potential to facilitate the availability of safer and more effective health products, to guide dose selection and to enhance their benefit/risk ratio, where the benefits should outweigh the risks. While it may not always directly benefit the study participants who are providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed during such researches. With the development of biomarkers, patients are now benefiting from retrospective biomarker research conducted on samples collected from previous clinical trials. One example is the EGFR antibody drugs cetuximab (Erbitux) and panitumumab (Vectibix) which highlights the value of KRAS status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug [2].

The risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns. Physical risks associated with biomarker sample collection in clinical trials can be characterized a negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support other primary trial objectives, and some added risk where the sampling procedure would otherwise have not been performed as a main component of a trial [2].

Together with the regulatory conditions discussed above the ethic of human research including those with biomarkers should respect the Nuremberg Code which is a set of research ethics principles for human experimentation set as a result of the Nuremberg trials at the end of the Second World War [25] and the Declaration of Helshinki [26] which implies respect for the individual, their right to self-determi-

nation and the right to make informed decisions regarding participation in research, both initially and during the course of the research. The investigator's duty is solely to the patient or volunteer and while there is always a need for research, the subject's welfare must always take precedence over the interests of science and society, and ethical considerations must always take precedence over laws and regulations [25-26].

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