WORLDWIDE CLINICAL TRIALS

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ASSURING PATIENT ADOPTION DURING BIOSIMILAR DEVELOPMENT AND COMMERCIALIZATION

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Successful clinical development and commercialization of small molecules and biologics require that investigators, sponsors, and patients collaborate to preemptively facilitate study design, execution, and transition to commercialization. Indeed, a patient's acquiescence to protocol-mandated procedures will dictate whether a program can be executed to predictable milestones and timelines and ultimately successfully transitioned into a clinical setting.

Although patients make the most critical personal investment in a treatment decision, they may be inappropriately perceived as passive elements in the biosimilar developmental process if the "value proposition" places undue emphasis on economic drivers, rather than the psychosocial variables that ultimately dictate usage. Despite a substantial body of literature on the technical aspects of biosimilar development, as well as regulatory guidelines and expert opinions,[1-8] [FDA Quality 2015, FDA Scientific 2015, EMA Guideline on Similar 2015, EMA Clin/Nonclin 2015], only recently have patient-related perspectives been examined. Publications on this most important topic are scant.

Factors driving perceived value from a patient's perspective for biosimilar products are likely as multivariate as those for generic small molecules (e.g., personal expense, interchangeability with the originator product). Additionally, given the complex manufacturing process and the nature of clinical efficacy or safety measurements used during biosimilar development, adherence to the originator compound ("brand loyalty") may become a dominating moderating variable influencing patient interest. The concept of "brand loyalty" is one which is familiar within the commercial sector as it embodies patient sentiments that foster reassurance from using only a known, approved chemical or biological entity for clinical care. Patients will consistently purchase products from preferred brands, regardless of convenience or price. Finally, still-evolving concepts for biosimilars, such as "fully interchangeable," may be difficult for patients to understand and therefore accept. These concepts are quite different from commonly accepted notions of "equivalency" based on experience with small molecules.

PATIENT OUTLOOK ON GENERICS AND BIOSIMILARS

Of course, generic drugs have been available a good deal longer than biosimilars, whether one considers the start of that industry to be in 1888, when the American Pharmaceutical Association published the National Formulary to "help prevent counterfeiting of branded products" or in 1992 when the Generic Drug Enforcement Act was effected [Hornecker 2009]. Accordingly, there is a wealth of literature examining the variables that influence patients' perspectives on generic small molecules. Although there are moderating variables, these reports provide a foundation for anticipating patients' perspectives on biosimilars, and designing development programs that would incorporate those sentiments into the fabric of the experimental and program design. Formal surveys using convenience sampling have revealed beliefs about efficacy, safety, and cost, as well as preferences for personal use of generic medications in the US,[9, 10] in Japan,[11] Australia,[12] Portugal,[13] and Malaysia.[14]

All surveys uniformly indicated that patients believe generics are less expensive and offer better value than brand-name drugs. However, the same patients are not eager to use generics personally, as illustrated for example by a US survey[9] with 1,047 respondents. Fifty-six percent stated that Americans should use more generics, but only 37.6% expressed a personal preference for generics. This common patient position — "Generic medications for you, but brand-name medications for me" — is also the meaningful title of an article reporting the results from a survey of 172 women enrolled in Tennessee's Medicaid program.[10]

A survey for an insulin biosimilar is also illustrative,[15] as it explores manifest and latent issues that may affect patients' enthusiasm for biosimilars. In this convenience sample of 3214 patients with type 1 or type 2 diabetes, 27% labeled their willingness to transition from an originator to a generic ("sometimes called biosimilar") drug "definite," 39% labeled it "likely," 13% "unlikely," and 4% "definitely not" (17% were unsure).

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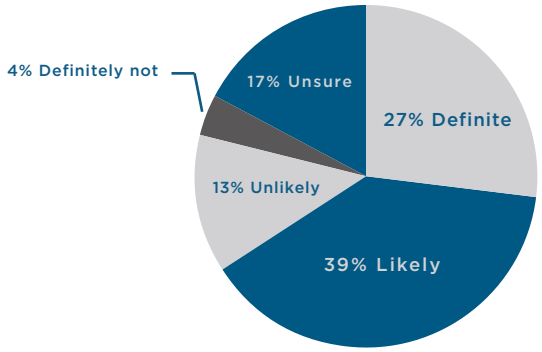

*In this convenience sample of **3214** patients with type 1 or type 2 diabetes, respondents labeled their **willingness to transition from an originator to a generic** ("biosimilar") drug.*

RESPONDENTS MENTIONED THE FOLLOWING AS CONTRIBUTING TO A NEGATIVE PERCEPTION OF GENERICS/BIOSIMILARS

- Proven track record of brand-name insulin currently in use
- Lack of a proven track record for biosimilars
- Current personal satisfaction with their particular insulin ("I do not trust things I do not know when it comes to my health.")
- Past bad experiences with generic medication
- Allergic reactions to various insulins
- Lack of trust in generic medications in general or biosimilars in particular.

Across all of the surveys mentioned above, the main factor associated with willingness to accept generic substitution was the patient's depth of understanding of the characteristics of the generic medicine in relation to the originator product, and that discussion must occur with a healthcare provider. Thus, it is the interaction with a healthcare provider which strongly dictates subsequent compliance.

PATIENT VIEWS ON BIOSIMILAR TRIAL ENDPOINTS

During the biosimilar development process, choice of clinical measures and manner of assessing outcomes impact a patient's decision regarding trial participation. The potential lack of clinical equivalency to the originator can jeopardize patient interest in a trial, depending on the trial endpoints. For example, the investigational program for a biosimilar filgrastim was adequately characterized from a regulatory perspective with pharmacokinetic/pharmacodynamic (PK PD) studies in normal volunteers, one comparative study involving patients with similar PK/ PD outcomes, and a commitment to conduct post-marketing surveillance via a registry. In addition, patient participation was encouraged by the use of short-term supportive care with an unambiguous laboratory endpoint (neutropenia), and easily measurable severe neutropenia that might occur after an established chemotherapy regimen.[16] In this scenario, a clear short-term endpoint, which could be unambiguously detected and interpreted, provides convincing evidence of effectiveness which would obviate concerned of longer-term exposure.

In contrast, in studies of biosimilar monoclonal antibodies in oncology, the use of a proxy for overall survival (such as progression-free survival or time to tumor progression) may be perceived as problematic by patients,[17] even if fully acceptable from a regulatory perspective.[18] These proxy endpoints insufficiently mollify patient concerns regarding comparability. While they speak to fundamental product attributes influencing disease progression and morbidity, they fail to directly address the patient's critical interest—which is of course mortality. Thus surrogate outcomes can weigh heavily on a patient's decision to accept possible exposure to a biosimilar versus a branded product as part of a development program and also during post-marketing studies. Additionally, even with an agreement to participate, there remains the potential for long-term

safety problems with clinical consequences which cannot be measured during the relatively short studies used to establish a biosimilar registration. This level of uncertainty will impact the informed-consent process for both initial trial participation and a switch in therapy, should market authorization be granted.

BIOSIMILAR TERMINOLOGY & CONCEPTS: PATIENT EDUCATION AND ADOPTION

Patients do consider potential similarities and differences between generic and branded medications.[9] Their perceptions in this regard emphasize the importance of patient education about biosimilars versus originator products, both in clinical practice and in clinical trials. Innovative therapies are often introduced with a companion patient-education program, especially in chronic diseases, and this approach to biosimilars also would benefit patients.[19] However, given the potential for subtle differences in efficacy and safety as well as product characterization as either a "biosimilar" or an "interchangeable biological product," educating patients about biosimilars may prove to be particularly challenging.

More broadly, this unique terminology is likely to obscure more than inform the development and commercialization process and has not been fully clarified by Regulatory agencies, despite multiple guidelines and related documents[20] [FDA Quality 2015, FDA Scientific 2015, EMA Guideline on Similar 2015, EMA Clin/Nonclin 2015]. Patients will need to transition from the concept of "equivalency" with which they are familiar to the concept of "fully interchangeable biological product" which may have a more obscure implication due to the use of this technical phraseology. This transition is likely to be difficult. Patients attempting to render an informed consent prior to randomization in a clinical trial, or to engage a new treatment option suggested by a provider, are disadvantaged.[21]

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THE COMPANION PATIENT EDUCATION PROGRAM

The World Health Organization (WHO) recognized the utility of patient education in a 1995 article describing their role in promoting it,[22] and again in a 1998 report detailing how a training program for healthcare providers in a therapeutic patient education program might be constructed.[23] WHO recommended: strengthening therapeutic effect by using patient education; making patient education a critical component of all patient management by all healthcare providers; and assessing the outcome of patient education.

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The validated example of the importance of companion patient education programs is represented by the inhalable insulin opportunity — even if not truly a biosimilar but an innovative formulation of a biologic — where inconsistencies in either pharmacology or compliance would have significant patient impact. In October 2007 Pfizer revealed that after an assessment of the financial performance of Exubera, as well as its lack of acceptance by patients, physicians and payers, it had decided to exit the product.[24] In contrast, Afrezza®, the second inhalable insulin product on the market, was expected to succeed where Pfizer's Exubera failed. The Sanofi and MannKind's Afrezza marketing strategy planned a more direct patient focus, encompassing processes like targeting patients, improving access, increasing awareness. This patient centric approach included a Coach program called Afrezza® COACH Diabetes Education Program[25], in which patients could enroll. This program provided:

- Personalized diabetes management and support
- Product training and emails containing helpful tips and important information
- Free education sessions, online or in person, on how to use the product and remain compliant with the treatment plan

REDEFINING VALUE THROUGH PARTICIPATORY RESEARCH

Although patients should be engaged with education and promotion during commercialization, it is the continuous process of engagement across the research and approval spectrum which is key to assuring that medical products will be characterized by acceptable patient adoption. One of the major barriers to recruitment and enrollment of patients in the studies is patients' lack of awareness about clinical trials.[26] However, equally critical are efforts which enable incorporation of the perspectives and concerns of patients and patient partners (i.e. advocacy groups) into the research designs—in essence, providing input on benefit and risk considerations during the product development strategy.

Managing diverse perspectives, encompassing multivariate approaches for patient engagement, facilitating communication among key stakeholders, and circumventing uncertainties around information used to describe product attributes presents a formidable challenge. In addition, the heterogeneity of patient populations likely approached and the multiple voices who may speak for the patient (for example, group and individual input) must be considered. This dynamic suggests that consent forms need to be revised to include what a patient needs to know to make informed decisions based upon educational precepts. Additionally, following approval the same concerted technique is required to assure patient adaption. Failure to consider sociodemographic variables influencing acceptance of new medication has been demonstrated for novel chemical entities[27], even when product attributes provided a compelling database for patient utilization.

Including the patient perspective in study design such as visit structure and the burden associated with the assessments and in formulation of the consenting process is essential for an effective drug-development strategy. This approach has been successfully employed in various therapeutic areas. For example, community based participatory research networks in oncology[28] offer concepts[29] that might be incorporated during biosimilar development. Including the patient perspective in the study design considerations enhances compliance, and ensures that outcome measures provide actionable data to patients, caregivers, and coordinated care networks.

Additionally, a large body of literature might be used to determine the emotional weighting that patients and caregivers will apply to patient specific outcomes. These types of data are derived primarily through observational research. Since drug development is increasingly moving toward an integrated program of interventional and observational studies, including patient perspective is a highly complementary objective[19]. Of note, the 21st Century Cures Act (enacted July 13, 2015) highlights the the diversity and hierarchy of evidence considered at the time of a drug's approval. Amongst many options, budget impact models, companion cost-effectiveness evaluations, and patient specific preferences and outcomes increasingly may influence the adoption of biosimilar products at the time of marketing under an umbrella of "competent and reliable scientific evidence," which the 21st Century Cures Act implicitly endorses[30].

Clinical development of biosimilars is increasing in a number of therapeutic areas (oncology, neurology, and immune mediated inflammatory disorders predominately). Clinical data may be needed to address uncertainty after analytical studies confirming product attributes and functional studies confirming pharmacological effects have been completed. Anticipating this need during the clinical development process creates a point of differentiation commercially, assuring easier acceptance from physicians, payers, as well as patients and their advocacy groups. These clinical marketing studies which would inform the variables dictating patient adoption can exploit a wealth of observational research options—with diverse patients and outcomes to serve as a template for framing product introduction.

CONCLUSION

Among the many stakeholders in clinical development, the patient is unarguably the most important. In a literature replete with references to personalized medicine that is tailored to variations in genetic and disease related phenotypes, the unique challenges associated with adoption of biosimilar products emphasize the importance of incorporating sociodemographic elements into the design of proposed clinical programs. The adoption of new therapeutics results from interactions between patients and healthcare systems in a mosaic wherein scientific data must be congruent with cultural and ethnic perceptions of medication and health status. Neither a regulatory strategy facilitating approval, evidence of utility in well-controlled trials, nor the existence of unmet need based on epidemiologic data can assure acceptance by patients and physicians of approved therapy in the absence of values that are relevant to the targeted population. Indeed, a patient's acquiescence to protocol-mandated procedures will dictate whether a program can be executed to predictable milestones and timelines and the results become a harbinger of successful transition into a clinical setting.

In biosimilar development, despite a substantial body of literature as well as regulatory guidelines and expert opinions, only recently have patient-related perspectives been examined, and very little data exist that systematically evaluates potential barriers to adoption. Yet, patient-perceived differences in efficacy or safety may exist during the development of, or the commercialization process for, biosimilar drugs that can be informed with experiences using generic, small-molecule drugs at least across principal domains. Therefore there is a strong need of embedding patients in the clinical trial development process using methods that have been articulated for "participatory research."

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