



editorial



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Beyond biomarkers in drug discovery and development

Introduction

The pharmaceutical industry has always sought to develop drugs that meet the basic clinical needs of treating symptoms and disease. Previously, many first-in-class drugs developed new multi-billion-dollar markets by targeting large populations. Gain marketing authorisation was often synonymous with gaining

market; this is no longer a certainty. Today, most new drugs compete against numerous therapies, including nonpharmaceutical options. To create new value these therapies need to provide benefits beyond existing therapies, and perhaps serve stakeholders differently to the prescribing physician and patient.

Looking for new value, pharma organizations have invested in identifying patient subgroups with superior biological responses to a specific new molecular entity [1,2]. Numerous investments focus on identifying novel biomarkers and companion diagnostics for personalized medicine [1]. Astonishing technical developments (genomics, proteomics, metabolomics) have fueled biomarker research [3,4], but progress is slow [5]. Until the tools of research improve, pharma companies need other ways to boost pharmaceutical productivity and create value; modern design methods might serve this role.

The pharma industry is not the first maturing industry to experience gradual commoditization, shifting customer requirements and pressures to increase productivity (information technologies once created value through technical performance, but now promote ease of use, mobility and connectivity). Complementary to finding biomarkers and companion diagnostics, one can create value by deeply understanding the context of use of new products. Personalized medicine which recognizes the individual characteristics of each patient certainly considers all the elements of patient care when tailoring individual treatment: usability, access, affordability, among others. Thus, knowledge and insights gained from human-centered research could provide keys for creating unique value.

Because investments in personalized medicine are driven partly by new demands from consumers, taking a human-centered approach to value creation makes sense. Patients desire treatments that integrate into their lifestyles and serve their aspirations (Fig. 1). This is consistent with known hierarchies of need [6] where early solutions meet basic requirements. Today, there are many new needs and stakeholders: caregivers have important roles; new buyers seek sensible alternatives; physicians want patients to succeed (against burdens of training, complexity and adherence). In addition, health authorities can update standards for safety and efficacy.

Adjacent to the insights for R&D provided by biomarkers, there are numerous human-centered insights that pertain to individuals, including knowledge of lifestyle preferences, care-giving

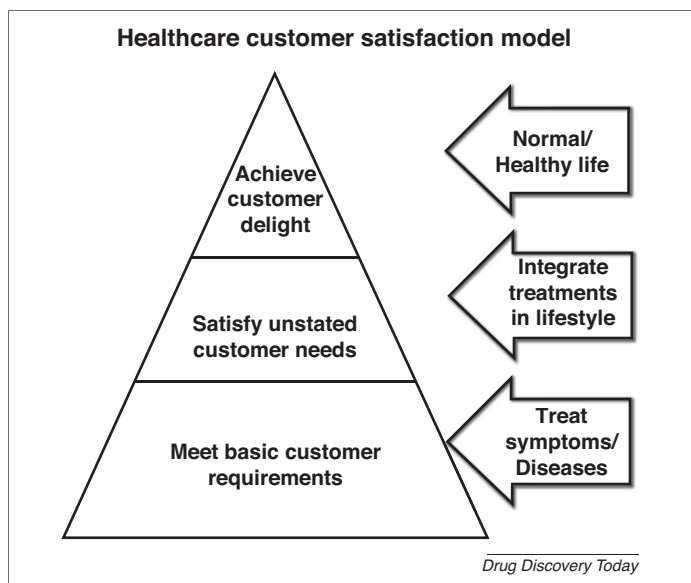


FIGURE 1

In today's healthcare market the customer measures success in more ways than clinical outcomes. Despite large investments in R&D it has proven difficult for many pharma companies to meet the increased demands for drugs that integrate well into specific lifestyle and support patient aspirations to live normal lives.

arrangements, desirable dosing regimens and management of side-effects and co-morbidities. Biomarkers and human-centered insights can figure into a target drug profile and guide development; for example recognizing that giving medication to a pre-teen child could guide developers toward a dosing format suitable for children's tastes and bodies, as well as parent and/or school schedules. Addressing such factors in discovery and development can significantly increase market acceptance; neglecting these factors could squander a drug's potential. Given the changing landscape of healthcare, and new demands from users and health systems, successful future drugs will integrate attributes from biomarkers and human-centered insights to provide optimal benefits for stakeholders. There is evidence that this approach can create value (Box 1).

Human-centered research can guide development and increase productivity

The challenge exists to translate human insights into products and features, and to incorporate insights much earlier in the development process. The goal is to focus research (greater efficiency during development) and establish real value when the molecule reaches the market (greater demand by meeting real needs). Just as the identification of biomarkers can lead to quantifiable tests and indicators, the identification of human-centered insights can suggest valuable characteristics of a new drug. These human insights can be subjective and qualitative in nature, including the insights mentioned previously, along with user preferences about style, mobility and social behavior.

The human-centered design process can reveal opportunity

Human-centered design research can uncover what is really meaningful to people – their needs, desires and aspirations – by testing and clarifying assumptions about users. Whereas the purpose of

most scientific research is validation of a hypothesis (or endpoint), design research typically seeks inspiration by collecting new perspectives (for later validation). The outcomes of design research are often new hypotheses about human behaviors and needs, which developers can probe. Scientific and analytical methods are excellent tools when only assumptions are clear. When assumptions are less clear, as is often the case with human issues or unfamiliar innovations, design tools offer a strong way to clarify assumptions and gain qualitative understanding of issues – and thus efficiently focus future analysis [7,8].

The human-centered design process starts with deep empathy for users, and concrete data from interviews and observations. In-field observations overcome prejudices, clarify context and collect detailed stories and evidence. Specific, vivid stories – not abstracted summaries – can produce original insights, even with very small user samples (a user sample of $n = 1$ is sufficient to illustrate that medications for arthritis should not require a strong grip). Empathetic observations help avoid pitfalls that are well known to user researchers: that people often do not (i) do what they are expected to do, (ii) do what they are told to do or (iii) do what they say they did. From the user stories, the design process abstracts themes, principles and frameworks that describe the world of users, creating actionable scenarios of opportunity. After forming hypotheses, the designer will create prototypes, experiments and storyboards of promising concrete concepts that researchers can bring back to users to confirm their value – or build better ideas. The process is iterative, generating many ideas and constantly improving them with new evidence from user feedback.

The identification of human-centered indicators of value might start with a promising molecular pathway that acts on a biological system (hunger, weight, metabolism). From this, one can postulate successful drug profiles, and then build stories about how these drugs integrate into the lives of all the stakeholders. Sharing these stories with patients, caregivers and physicians is a rapid, low-risk way to collect feedback about the potential impact of an idea, and what specific product features are necessary to create this impact and value.

User-research can have a bottom-up or top-down human-centered focus

The bottom-up approach relies on early discussions and 'probes' with potential users to evaluate whether specific novel biological targets could provide a real benefit to specific users. The top-down approach requires user research to define new, attractive opportunities within a targeted customer segment. With user data, teams can define and direct research platforms to identify molecules affecting a biological pathway that could provide the desired benefit. Both approaches collect evidence about:

- the patient's daily life, challenges and concerns;
- how the patient and caregivers manage the disease (and co-morbidities);
- current alternative therapies and their limitations (including nonpharma therapies);
- common problems for patients and/or caregivers, and popular 'work-arounds'.

In the bottom-up approach, including human-centered criteria throughout discovery and development creates confidence that the science remains relevant for potential users, and that discoveries will

BOX 1

An example where a deep understanding of human behaviors combined with biological insights is the recently marketed class of glucagon-like peptide (GLP)-1 drugs for treatment of type 2 diabetes (T2D)

Exenatide, a twice-daily injection to control HbA1c (originally from Amylin and Lilly), competed with oral treatment alternatives. Despite being injectable, exenatide succeeded (partly by promoting weight loss), generating over US\$500 million in sales in 2011 (<http://www.drugwatch.com/byetta/>). Instead of shunning injectables in favor of orals, patients were willing to inject themselves twice daily, suggesting weight loss was also important to users while lowering HbA1c [11]. Subsequently, many companies accelerated development of their GLP-1 drugs, seeking improved pharmacokinetic properties for once-daily or once-weekly injection. Five years after exenatide, liraglutide (Novo Nordisk) appeared as a once-daily injection, capturing a majority share in many markets (<http://www.drugwatch.com/victoza/>). The next generation of products includes once-weekly alternatives. Time will tell if these products will capture significant market share from the daily options, acknowledging the user desire for fewer injections. Meanwhile, Sanofi launched once-daily lixisenatide (licensed from Zealand Pharma) [12], the profile of which provides significant postprandial glucose control [13], complementing basal insulins that control fasting blood glucose. Before lixisenatide, Sanofi had accumulated insights into patient and prescriber behavior through Lantus[®] (basal insulin glargine). Sanofi understood the potential of lixisenatide regarding postprandial glucose control, and also realized that many T2D patients on basal insulin were reluctant to take mealtime insulin for additional glucose control – and Sanofi targeted the development of lixisenatide for these patients. Recognizing the favorable potential of including a GLP-1 agonist with basal insulin, physicians have prescribed this combination ‘off-label’ frequently (at lixisenatide launch in Europe, ~40% of all GLP-1 agonist prescriptions paired with basal insulin). This early focus on human behaviors, combined with biological insights, helped place lixisenatide in a different competitive market to the providers of long-acting analogs. Further, beyond offering longer-acting versions of GLP-1 agonists, companies now focus on injections of the combination of once-daily GLP-1 with basal insulin (http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002647/WC500170171.pdf, http://www.sanofi.com/Images/33239_24062013_ADA_final_Web.pdf). This solution holds great promise for patients on basal insulin who need better glucose control, desire once-a-day injection or have concerns about weight gain. Pharma companies developing novel GLP-1 receptor agonists could have sought biological biomarkers to predict patient-specific responses to each drug, or sought formulations with fewer side-effects; however, the focus on human needs created significant new value and better patient care.

meet real needs (a therapy that meets a clinical endpoint does not guarantee its value in today’s crowded marketplace). Teams can refine these hypotheses throughout the discovery and development process based on new evidence (user-research, feedback and emerging key biological data). User-research can suggest key product attributes required for success – to differentiate a product among competitors, to solve a previously unmet need or to integrate the use of the product into someone’s lifestyle. Thus guided, teams can focus on specific *in vitro* and *in vivo* experiments that could demonstrate these promising specific attributes.

A top-down human-centered approach might involve collecting information about underserved needs among key customer segments, uncovering unexpected needs among patients, physicians and other stakeholders, and focusing research efforts to identify molecules with specific attributes that serve these needs. Data from the top-down process can guide initial target development, opening potential research avenues, uncovering insights from stakeholders outside the vision of an R&D organization and suggesting radical collaborations. Such collaborations can increase value through partnerships that bring new capabilities to products, and suggest strategies to coordinate care or share risk; a strategy already adopted by several companies [9,10].

With either approach to human-centered research, the molecular development process benefits from parallel human-centered research throughout the discovery and development phase. This suggests incorporating well-defined human-centered criteria and milestones inside the product development process. These milestones should co-exist with (not replace) existing business and technical milestones.

Human-centered user research can (i) increase the productivity of development teams by helping them choose the most useful potential medicines when there are many alternatives and (ii) help articulate real value to users for a given medicine. New value could result from features and attributes that are different to purely clinical results (i.e. attributes that support successful use, the circumstances of care or integration into larger therapeutic plans). By building a culture that supports human-centered research, R&D organizations can significantly augment their tools for guiding personalized medicine and create robust portfolios of products that users strongly value.

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