Accelerating development of scientific evidence for medical products within the existing US regulatory framework

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Growing access to diverse ‘real-world’ data sources is enabling new approaches to close persistent evidence gaps about the optimal use of medical products in real-world practice. Here, we argue that contrary to widespread impressions, existing FDA regulations embody sufficient flexibility to accommodate the emerging tools and methods needed to achieve this goal.

It is widely acknowledged that there is often a gap between the scientific evidence generated on medical products during clinical trials to support their approval or clearance and the evidence needed to inform their optimal use in real-world environments. Consequently, efforts to close this gap through methods that leverage real-world evidence have been a high priority for several years1–2. However, these efforts have been clouded by widely held views that current regulatory structures cannot accommodate a modern, robust and diverse evidence base, and that these regulatory structures are predicated on narrowly targeted premarket evaluations of medical products. We regard both of these views as misperceptions that need to be corrected.

Trials, the evidence gap and evolving standards

Industry expenditures on clinical research substantially exceed those of the US National Institutes of Health (see Further information), and the vast majority of trial participants are enrolled in industry-funded trials3. Thus, the primary driver of most clinical trials designed to evaluate medical products is industry’s need to achieve regulatory approval or support labelling changes.

In the modern regulatory era, trials conducted to gain marketing authorization often focus on demonstrating efficacy in controlled environments and in carefully selected populations. As a result, design attributes that evolved to ensure expeditious, clear answers to narrowly framed research questions can also raise questions about the applicability of findings to real-world medical practice. Over time, this has led to uncertainty about whether or how to use a given treatment; furthermore, the need for additional evidence to inform practice is seldom fully addressed in post-market settings. Discussions about solutions to these challenges often assume the need for two distinct sets of evidence — one to determine whether a product should be marketed, and another to determine how it should be used. However, this assumption does not accurately reflect historical and current evidence standards, which afford substantial flexibility for obtaining approval or clearance of medical products (see Supplementary information S1 (box)).

Informing decisions with the ‘totality of evidence’

The FDA considers the totality of evidence when evaluating the safety and effectiveness of new drugs. This phrase reflects the nature of drug development, with each successive piece of data building on prior data to provide the quantity and quality of evidence needed to adequately assess risks and benefits. Data from a study are always assessed within the context of other available data, never in isolation, and data from different studies are considered based on the reliability of a given study result. Another element of flexibility includes the ability to use an understanding of the therapy, the disease, treatment alternatives and patient preferences to make discrete decisions about marketing and labelling with full recognition that the evidence bases for the disease and for alternative therapies are constantly changing.

Pivoting from approval to real-world use

Ubiquitous electronic health records, effective use of claims data, quality registries and the focus on ‘learning health systems’2 are changing clinical trials in ways that can, if properly harnessed, help to inform the real-world use of products at a much lower cost1. This in turn creates opportunities for realizing benefit and avoiding harm. For example, some therapies now known to show major benefits in broad populations, such as statins and inhibitors of the renin–angiotensin–aldosterone system, took many years to gain acceptance in practice (and to have the evidence supporting their benefit firmly established). Conversely, a recent study4 indicates not only significant

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off-label prescribing in clinical practice (an unsurprising finding), but also a correlation between off-label prescribing and increased rates of adverse drug events. Intriguingly, the risk of such events was increased when off-label use occurred in circumstances in which there was a lack of strong scientific evidence to support that use.4

We believe that by adopting approaches in which initial marketing studies (or those initiated soon after marketing) ‘pivot’ towards broader trials that evaluate therapies in populations and settings that more closely resemble clinical practice, researchers can help ensure that patients and providers are as informed as possible and that risks are identified by regulatory review, appropriate labelling and incorporation into clinical practice guidelines. So, how can we enable this pivot?

**Reimagining evidence generation**

We believe that recognition that the evidence needed to support regulatory approval or clearance and the evidence needed to inform treatment decisions are both part of a single continuum creates a powerful direct incentive for manufacturers and/or study sponsors to appropriately evaluate the benefits and risks of a product in real-world conditions and among the groups of patients likely to be treated once the product is marketed. Moreover, a transition to this new paradigm is possible now, under a regulatory schema whose standards—including the totality of evidence construct described above—already embody the flexibility needed to accommodate evolving methods and technologies.

This can be illustrated by examining one situation in which a flexible approach incorporating the totality of evidence can further inform regulatory decision-making and illuminate the optimal use of a product in practice. The monoclonal antibody daratumumab, a treatment for multiple myeloma, was recently evaluated under accelerated approval by the FDA, in which approval may be based on a surrogate end point reasonably likely to predict clinical benefit if that drug treats a serious condition and fills an unmet medical need. The pivotal trial to support approval was a single-arm, phase II trial of 106 individuals who were refractory to multiple previous regimens; study participants received 16 mg kg\(^{-1}\) of daratumumab until disease progression. The final analysis showed an overall response rate (ORR) of 29%, with a median time to response of 1 month and a median duration of response of 7.4 months. Further support for efficacy was provided by a phase I/II dose-ranging and safety study, which showed an ORR of 36% for the study cohort that received a 16 mg kg\(^{-1}\) dose (\(n = 42\)). Both studies were open-label and neither had a concurrent control group. Additional randomized trials were under way at the time, and data from these trials have recently prompted labelling enhancements on the basis of a composite end point of disease progression and survival (see Further information). Answers to major questions such as the multiple combinations that can be used, optimal duration and dose of therapy in subpopulations, and long-term safety are likely to come from real-world evidence sources. Applying a flexible approach in this context enables a promising treatment for a serious condition to reach patients quickly, while continued rigorous evaluation provides an increasingly clear picture of risk and benefit, and qualitative detail supplied by real-world data sources helps to better specify its optimal clinical application.

We recognize the challenge in achieving this cultural shift, especially given the sensitivity to the maintenance of perceived or real standards. The current paradigm is heavily weighted towards systems that focus on elements needed for precise answers to narrow questions, and we are just beginning to grapple with defining quality in ways that allow us to accurately characterize product performance in real-world settings that include diverse and varied patient populations and practice patterns. The concept of ‘quality by design’ as developed for clinical trials by the Clinical Trials Transformation Initiative provides one framework for this effort. Clearly, any change in approaches to research on medical products raises concerns about uncertainty and impact on business models for medical product development and the accompanying major investment of time and resources. It will also require substantial effort within the FDA and interaction with the medical products and clinical research industries, providers, health systems and patients themselves, who have the most to gain from better information about the use of medical products.

However, we believe that routinely integrating these separate worlds into a continuum that progressively demonstrates that a therapy can be used safely and efficaciously, but pivots as quickly as possible to producing evidence to accurately inform clinical use, will yield a comprehensive understanding of how to use medical products in practice—an understanding that can be incorporated into product labelling. This could also facilitate wider market access for products whose benefits are shown to outweigh risks, while simultaneously enabling ineffective or dangerous uses to be identified and avoided. As we note, an important element of an overall approach is the use of broader trials measuring relevant clinical outcomes, as currently allowed by existing authorities and increasingly encouraged by the FDA.

We welcome collaboration with industry, practice, academia and patients to change the system in an efficient manner to close vital gaps in evidence, beginning with improving the relevance of trials conducted for regulatory approval, clearance and labelling changes.

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The authors declare competing interests: see Web version for details.

**FURTHER INFORMATION**


Darzalex (daratumumab) prescribing information: www.janssenmd.com/pdf/darzalex/DARZALEX_PI.pdf

**SUPPLEMENTARY INFORMATION**

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