



# The next frontier of drug development and approval

## Executive summary

Future progress in biopharma research and development (R&D) hinges, in part, on reducing regulatory uncertainties. Many biopharma companies and regulatory agencies around the world are continually exploring ways to evolve their processes, programs, and standards to reflect new scientific and evidentiary models occurring in drug development. This paper examines three areas that multiple stakeholders consider to have the potential to substantially improve the drug development and approval process. If biopharma companies, regulators, and policymakers find common ground on the following areas, it could enable a smoother pathway to the next frontier of drug development and approval:

- Benefit-risk assessment: enhancing transparency among regulators and between regulators and biopharma companies.
- Patient-reported outcomes (PRO): encouraging continued stakeholder collaboration to develop procedures and policies around the use of patient-reported instruments and delineating pathways for patient involvement in the drug development process.
- Real-world evidence (RWE): identifying leading practices for RWE use and interpretation, and establishing a multi-stakeholder task force focused on standardizing data to make the evidence reproducible, interoperable, and operational for regulatory purposes.

Combined, the United States' Food and Drug Administration (FDA), the European Medicines Agency (EMA), and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) regulate most of the global pharmaceutical market. These agencies have implemented a number of policies and programs over the years to keep pace with scientific advances and drug development methods, and to work collaboratively with manufacturers to bring innovative new therapies to patients as soon as possible.<sup>1</sup> The agencies also work closely with one another in certain areas.<sup>2</sup> If regulatory agencies align to move these priority areas forward, and provide clear guidance for the biopharma industry to follow, the result could lead to significant change to the global regulatory environment. While there is general consensus that total regulatory alignment may never be achieved, or that such alignment would not be desirable across every country, many stakeholders agree that increasing alignment in certain areas of the drug approval process may produce positive results for the consumer, industry, regulators, and public health.<sup>3</sup>



## Introduction

Before a new drug enters the market, it undergoes an arduous, time-consuming, costly, and unpredictable R&D process. Government agencies then provide regulatory oversight to assure its safety and efficacy. Throughout this process, biopharma companies face uncertainty around complex science, regulatory hurdles, coverage decisions, and policy changes (see sidebar) which, in turn, may lead to inefficiencies in drug development and approval.<sup>4</sup> For instance, if products are approved in some countries and not others, consumers' access will vary accordingly.<sup>5</sup> Consumers may be confused as to why a given drug is considered safe and effective in one country and not in another.

Several organizations are making progress in aligning drug approval requirements. One example is the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), formally known as the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceutical Products. ICH brings together the biopharma industry and drug regulatory authorities of Europe, Japan, and the United States, and facilitates collaboration to develop Tripartite Guidelines, which the regulatory agencies agree to implement.

While worldwide regulatory harmonization is likely not possible – or even desired – given the need to keep the drug approval process flexible and resilient, stakeholders agree that more can likely be done to encourage alignment, particularly as regulatory agencies consider policy changes to integrate new sources of data and incorporate the patient perspective.

### Biopharma areas of uncertainty<sup>6,7</sup>

The global biopharma industry operates in an extremely challenging environment. Biopharma companies are expected to grow revenue and boost shareholder return despite ever-increasing R&D costs, slow time-to-market, and pressure by governments, health care providers, and health plans to control costs and improve outcomes. A dynamically changing scientific, regulatory, and business landscape is requiring companies to re-evaluate their traditional business and R&D models to:

- **Demonstrate value.** Widespread efforts to slow health care spending growth, reduce variations in care, and engage consumers in self-care are increasing emphasis on demonstrating a drug's value. As part of this focus, comparative effectiveness research is starting to play a role in product adoption and market uptake. In the future, products not proving to be more effective than their competitors may struggle to generate demand or attain reimbursement.
- **Bend the cost curve.** Cost-conscious governments and other health care payers are imposing price controls and increasing incentives for physicians and patients to use less-expensive generic drugs and biosimilars.
- **Maintain regulatory compliance.** The evolving regulatory landscape continuously challenges the biopharma sector. Although all regulators focus on patient health, safety, and privacy, the way policies are developed can vary widely from country to country.

## Stakeholder priorities

Biopharma companies and regulators are exploring ways to evolve the drug development and approval process and to develop guidance and standards that take into account scientific innovations and evidentiary models. Deloitte has identified three stakeholder priority areas to consider – benefit-risk assessment, patient-reported outcomes, and real-world evidence – based on the following criteria:

- Multiple stakeholder groups (biopharma companies, regulators, consumer and patient advocacy groups, researchers and policy makers) are interested in learning how to better integrate these areas into the development and approval process.
- These priority areas have come up repeatedly in the literature and in discussions with stakeholder experts.
- These priority areas have been articulated in comment letters sent from multiple stakeholders, including industry, patient advocacy groups, researchers, and provider groups, in response to the House Energy and Commerce Committee’s 21<sup>st</sup> Century Cures initiative.

## Benefit-risk assessment

Benefit-risk assessment is the first priority area stakeholders have identified as having the potential to improve the drug development and approval process. Among suggested actions from stakeholders are developing a uniform policy statement, supporting pilot programs, and delineating pathways for consumer involvement.

**Background:** Benefit-risk assessment is the process of weighing a treatment’s risks against its related benefits. Stakeholders involved in drug development and approval must evaluate the balance between benefits and risks – the process is particularly critical for regulatory agencies. However, regulators traditionally have had to make their assessments based on the product information available at the time of submission, which can be limited. Although regulators strive to make a transparent, reproducible decision, this uncertainty can make it difficult for a broader audience to understand the rationale for the decision. Moreover, governments, researchers, and other experts are exerting pressure on regulators and the biopharma industry to increase transparency and clarity around benefit-risk assessment.<sup>8</sup>

## Findings on benefit-risk assessment from Institute of Medicine report and PCAST report

The 2013 Institute of Medicine (IOM) report on regulatory harmonization details how stakeholders from industry, regulatory agencies, researchers, and patient advocacy groups gathered to address the need for international harmonization of regulatory standards to support the development, evaluation, and surveillance of biomedical products. A key discussion point for the group was benefit-risk assessment. The IOM report:

- Called for a way to more effectively communicate benefits and risks associated with a particular product being tested;
- Noted how essential transparency is when making decisions and how uncertainties figure in the decision;
- Called for employing tools that facilitate a simple, structured, and systematic approach to assessing benefits and risks. Among these tools are a common lexicon and a common format for benefit-risk communication.

Findings from the President’s Council of Advisors on Science and Technology (PCAST) *Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation* highlight some of the challenges for regulators around benefit-risk assessment. The report also notes several ways to address uncertainty and to optimize the approval of drugs that have a favorable benefit-risk balance. These include:

- Better scientific tools, such as toxicity and benefit predictors, to improve regulatory decision-making by increasing the level of certainty about drug risks and benefits;
- Adequate statutory authority and clear interpretation of that authority for early approval of drugs based on indicators, such as disease-specific surrogate and clinical endpoints that have a high likelihood of positive therapeutic response in serious and life-threatening diseases with unmet needs, or early approval of preventive medicines in high-risk patients;
- Robust surveillance systems for collecting post-marketing data about the risks and benefits of medical products, including high-quality and interoperable electronic health records.

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**Opportunity for alignment:** To date, there is no universal approach or standard methodology to aid regulatory decisions on the benefits and risks of specific medicines. Stakeholders around the world are leading several initiatives to explore methods to help regulators make more structured, transparent benefit-risk decisions. Some of these methods use a qualitative approach while others use a quantitative approach that involves assigning weights to benefit and risk considerations. For example, in the US, the FDA has adopted a structured qualitative approach designed to support the identification and communication of key considerations in the agency's benefit-risk assessment.<sup>9</sup>

The FDA's work in structured benefit-risk assessment coincided with the EMA's benefit-risk methodology project,<sup>10</sup> which set out to identify decision-making models that can assess the benefits and risks of medicines more consistently and transparently, and make the assessment easier to audit. The EMA is also coordinating a collaborative European Innovative Medicines Initiative Project called PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium).<sup>11</sup> This initiative has a number of work streams, one of which (PROTECT Work Package 5) aims to develop quantitative methods to use in benefit-risk assessment, with a focus on the graphical presentation of benefit and risk data. These FDA and EMA initiatives continue to evolve. For example, the FDA implemented a staged approach to enhancing its benefit-risk assessment; the agency began piloting the framework using applications under review in 2012. The outcome provided valuable insight for the FDA and proved useful in drafting the fifth authorization of the Prescription Drug User Fee Act (PDUFA),<sup>12</sup> which gives the FDA the necessary resources to maintain a predictable and efficient drug review process.

As some common approaches are emerging among the various benefit-risk evaluation methodologies, quantitative statistical approaches are also evolving. The latter can synthesize and combine disparate data from many sources and present it in a structured fashion to aid decision-making. To further advance benefit-risk assessment, stakeholders should consider focusing on:

- Developing a uniform statement of policy, even if the methodology used to develop the policy is flexible: A transparent articulation of the benefits and risks considered when regulatory authorities make their final decision could provide the context for a structured discussion about the decision-making process.
- Continuing pilots to test different quantitative approaches to benefit-risk assessment: Such approaches could improve regulatory decision-making by increasing the level of certainty about drug risks and benefits. Regulatory, academic, and industry stakeholders should consider continuing to collaborate on developing such tools.
- Delineating pathways for patient and caregiver involvement: Regulatory agencies recognize the importance of involving patients in the scientific dialogue around drug approval and have introduced some programs to respond to this need. However, regulators should consider providing additional clarity on how the patient voice will be incorporated in benefit-risk decisions. One example is the FDA's Patient-Focused Drug Development initiative<sup>13</sup> under PDUFA V.<sup>14</sup> This initiative focuses on gathering patients' perspectives on a medical condition's impact on daily life and the available therapies to treat that condition.

### Patient-reported outcomes

Incorporating patient-reported outcomes is the second priority area stakeholders have identified as having the potential to improve the drug development and approval process. Suggested actions from stakeholders include developing harmonized reporting procedures, incorporating stakeholder input, and using consistent data-capture approaches.

**Background:** The FDA defines PRO as any status report on a patient's health condition that comes directly from the patient, without a clinician or other individual interpreting the patient's response.<sup>15</sup> PRO typically include information about health-related quality of life (HRQL), symptoms, function (disability), satisfaction with care, adherence to prescribed medications or other therapy, and perceived value of treatment. Stakeholders use PRO data to inform and guide patient-centered care as well as clinical and health policy decision-making.

**Opportunity for alignment:** The use of PRO data in drug clinical trials and label claims is regulated by the FDA and the EMA, but Japan's PMDA currently does not have such regulations. The FDA issued formal guidance that set standards for using PRO data to support product labeling claims and to assess clinical trial efficacy outcomes. The guidance is intended to increase the efficiency of discussions during the drug development process and to streamline the FDA's review of PRO instruments and the resulting PRO data-collection process during a clinical trial.

The EMA released a reflection paper on HRQL use in response to the FDA guidance. The agency is working to increase its interaction with patient and consumer organizations, and is revising its framework to incorporate patients' roles on scientific committees, their involvement in benefit-risk evaluation, and a strategy for training and support.<sup>16</sup> The PMDA has not issued formal guidance on PRO use for drug clinical trials and labeling. The agency strictly regulates information in the Package Insert (PI) but manufacturers may include PRO claims based on the research data supplementary information that they provide to pharmacists.<sup>17</sup>

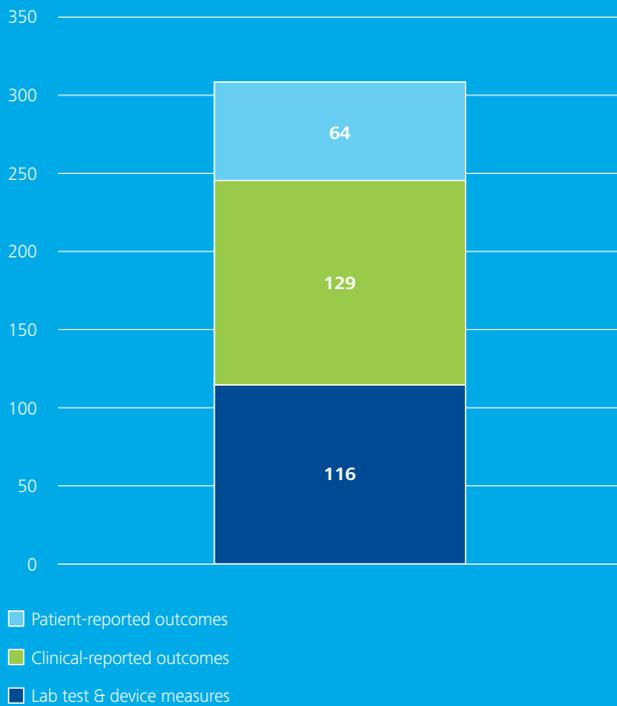


The growing number of clinical trial applications has encouraged the FDA and the EMA to consider PRO in the regulatory process and release guidance documents on their use. Both FDA and EMA have recognized the value of patient-centered measures in health outcome assessments and have expanded methodological aspects such as study design, statistical analysis, hypothesis testing, reliability, and validity of patient-centered measures. However, there are certain differences: The FDA has stated that all PRO, including HRQL, can be used as effectiveness endpoints in clinical trials and, in particular, for drugs to be licensed for chronic diseases (e.g., cancer, HIV). In contrast, the EMA does not assign the same weights to all the PRO measures. While the EMA accepts the core symptoms of a disease assessed by the patient as primary and secondary efficacy endpoints in registration trials, the agency's guidance regards the HRQL assessment as an optional endpoint of a drug's efficacy.

### Opportunity for greater PRO data use in label claims

In a study of 215 new drugs approved in the US from 1997 to 2002, 64 products (30 percent) included PRO data in the clinical trials section of the label as a measure of treatment benefits (Figure 1).

**Figure 1: Types of endpoints for 215 new drugs approved in the US from 1997–2002<sup>18\*</sup>**



\*Some products have more than one type of endpoint

PRO are not as commonly used as traditional clinician-reported outcomes (e.g., mortality, tumor response) or laboratory tests and device measurements (e.g., FEV1, HbA1C, blood pressure). However, 23 of the new drugs used only PRO endpoints as measures of treatment benefit, including antimigraine products and some drugs for pain relief; as well as antiepileptics, antinfluenza, and some drugs for allergic conjunctivitis. Other types of drugs that relied heavily (but not entirely) on PRO endpoints included anti-inflammatory agents, gastrointestinal agents, vaccines, and respiratory and urologic agents.

The lack of standardized procedures provides all three regulatory agencies – FDA, EMA, and PMDA – an opportunity to advance and harmonize their PRO-related guidance and standards. Accordingly, regulatory agencies that aim to generate and ultimately align their guidance and standards could consider:

- Developing and updating harmonized procedures around the definition of PRO measures, including HRQL, incorporated during their decision-making processes: New PRO instruments based on psychometric research could improve the quality of the data obtained. Agencies could encourage sponsors to incorporate PRO in the drug development strategy and in clinical trials, so that the data can be included in evidence submitted for approval and on labeling.
- Collaborating with stakeholders, including drug developers, investigators, patients, providers and caregivers, and PRO instrument developers to develop aligned procedures and policies around the use of PRO as part of clinical research: In particular, the PMDA should consider aligning any forthcoming guidance with the FDA and the EMA.
- Generating leading practices on how to incorporate patient-focused outcomes into R&D: Many stakeholders support incorporating patient input into the drug development process but strategies to incorporate the flood of available data and opinions are not clear-cut. Some biopharma companies are hiring staff to define these strategies and regulators are holding patient-focused workshops. Sharing leading practices between regulators and industry may help identify effective strategies going forward.<sup>19</sup>

#### **ADAPTABLE study: Incorporating patient outcomes and experience in a real-world setting**

The Patient-Centered Outcomes Research Institute (PCORI) was created by the Affordable Care Act (ACA) to work with health care providers and patient networks to increase patient involvement in medical research and promote comparative effectiveness studies. PCORI is looking at scientifically and clinically useful methods around patient-reported outcomes and real-world evidence. In 2015, PCORI announced it would fund the ADAPTABLE (Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-term Effectiveness) study to compare the potential benefits and harms of a low- and regular-strength daily dose of aspirin in patients diagnosed with heart disease. The study is designed to provide patients and providers with detailed information about aspirin therapy based on patients' personal characteristics, conditions, and preferences. Researchers also will compare the effects of aspirin in certain patient populations based on gender, age, and racial- and ethnic-minority affiliation, and in patients with certain health conditions. Rather than being conducted in specialized research centers under optimized conditions, ADAPTABLE is a pragmatic trial designed to confirm its results demonstrate real-world medical practice.<sup>20</sup>

## Real-world evidence

The use of real-world evidence is the third priority area stakeholders have identified as having the potential to improve the drug development and approval process. Specifically, regulatory bodies evaluating approaches to incorporate RWE could advance standards on this topic and make sure the standards are communicated to the biopharma industry. Also, convening a multi-stakeholder task force could provide useful input for the development process.

**Background:** Informed clinical decision-making requires synthesizing multiple sources of evidence. In addition, stakeholders need to understand the value of each type of evidence to advance health care quality.<sup>21</sup> While many in the biomedical world consider randomized controlled trials (RCTs) to be the gold standard of research, RCTs are expensive and time-consuming, and can have limited generalizability due to their idealized environment. RWE is health care data derived from sources other than randomized clinical/controlled trials. RWE sources include supplements to RCTs, large simple trials, patient registries, administrative claims, surveys, electronic health records,<sup>22</sup> and mobile health-generated data (e.g., smartphones, wearables, social media).

RWE involves a large and diverse patient population in real-world settings, and provides data on populations not included in RCTs. Multiple stakeholders – patients, payers, providers, industry, and regulators – would prefer to rely more on RWE in the drug development and regulatory process.<sup>23</sup> For industry, use of RWE could reduce RCT costs by accelerating patient selection and enrollment. Further, RWE could enable a better understanding of where a product in development may fit into future treatment paradigms, based on outcomes for competitive treatments.

If regulatory agencies would allow RWE for use in pre-authorization decisions, it may accelerate changes to the traditional evidence hierarchies (i.e., where randomized controlled trials are considered the best data sources), potentially creating more diverse approval pathways for new indications.<sup>24</sup> It is important to note that introducing new data into an already complex drug approval process likely will be challenging for industry and regulators. The FDA has been working to address this issue for many years. One example is the Sentinel Initiative, a national electronic system the FDA launched in 2008 that aims to transform the agency's ability to track the safety of drugs, biologics, and medical devices once they reach the market. Another example is the Innovation in Medical Evidence Development and Surveillance (IMEDS) program, which sits within the Reagan-Udall Foundation (RUF) for the FDA. This public-private partnership is designed to help the FDA, industry and clinicians to improve patient care and medical product safety by using an increasing body of evidence. The IMEDS program addresses several critical needs, including:

- Developing methods for using electronic health data for safety assessments and broader purposes;
- Establishing a long-term research agenda and corresponding governance structure to address the methodological needs of Sentinel and other stakeholders;
- Leveraging Sentinel tools to help answer questions about the safety and effectiveness of interventions.

Two other initiatives illustrate multi-stakeholder interest in increasing consensus and action around RWE throughout the drug development and assessment life cycle: the US House of Representatives' Energy and Commerce (E&C) Committee's 21<sup>st</sup> Century Cures Act and the European Innovative Medicines Initiative (IMI). The 21<sup>st</sup> Century Cures Act<sup>25</sup> aims to develop or update regulations and incentives that govern the discovery, development, and delivery of US medical innovations. The legislation calls for the FDA to establish a program to evaluate the potential use of RWE to help support the approval of a new drug indication and to support or satisfy post-approval study requirements. Agencies will have to determine what types and sources of RWE to incorporate, as well as the stakeholder implications, if the new drug development pathways are adopted.<sup>26</sup>

The IMI, Europe's largest public-private initiative, aims to speed-up the development of better and safer medicines. IMI's three-year GetReal project, launched in January 2014, addresses questions about incorporating RWE in drug development and relative effectiveness assessments.<sup>27</sup>

#### Industry example of incorporating RWE in drug development

Astellas' TRUMPET (Treatment Registry for Outcomes in CRPC Patients) study is a prospective observational registry study designed to better understand the needs and treatment patterns for US patients with castration-resistant prostate cancer (CRPC). The registry will enroll and evaluate 2,000 patients diagnosed with CRPC from sites across the US, and collect data from patients' primary caregivers. TRUMPET is assessing patient care patterns and does not evaluate any specific treatment or medication.

**Opportunity for alignment:** Current regulatory guidelines for RWE center on post-approval activities, such as fulfilling mandatory Phase IV post-marketing safety and pharmacovigilance commitments and drug utilization studies. Internal agency discussions about incorporating RWE before drugs are approved are in the early stages; however, new policies and guidance addressing RWE are beginning to emerge.<sup>28</sup>

To fill the need for detailed guidance on RWE across the drug development and assessment life cycle, stakeholders have asked regulatory agencies for additional guidance, and are seeking alignment on:

- Advancing standards on RWE use and interpretation: Specifically, guidance is needed around incorporating RWE in pre-approval, including to support the approval of a drug's use for a new indication (label expansion);<sup>29</sup> and in post-approval, including to support or satisfy required, post-market studies and provide product safety data and monitoring.<sup>30</sup> The three agencies could consider harmonizing guidance around RWE relevance during different drug development and assessment phases, and when updating their evidence hierarchies.<sup>31</sup>
- Establishing a multi-stakeholder task force to focus on standardizing data: The task force should represent regulatory agencies, drug companies, patient groups, researchers, health care providers, and payers, and should emphasize standards for the language and definitions of common terms, and coding; standards to secure the data and protect patient privacy; and statistical methodologies for data analysis.
- Collaborating with other stakeholders including medical experts and consortia to develop the guidance: The goal is to make RWE standard, reproducible, interoperable and interconnected, and operational for regulatory purposes. Public private partnerships such as the RUF provide examples of multiple stakeholders working together to advance RWE use and interpretation.

### Potential impacts of advancing these priority areas

How might the stakeholder priority areas discussed above affect the clinical development and regulatory approval process? Could these and other interventions leverage new, robust data sources to make the process more efficient and “bend the curve?”

Numerous health care stakeholders are interested in finding ways to increase drug approval productivity, including patients who want to see new, innovative products in the marketplace. Many biopharma companies, regulators, researchers, and policy makers are focused on how to increase the likelihood of approval for drug candidates by streamlining the clinical trial process with accelerated research and evaluation programs.

When examining the causes of attrition late in the drug development process, data suggests that one contributor is lack of transparency around regulatory requirements; specifically, early-stage benefit-risk assessment. Late-stage failures are in direct conflict with a drug sponsor’s desire to “fail fast, fail cheaply,” although roughly 50 percent of drugs face challenges at this juncture, with many requiring multiple review cycles.<sup>32</sup> Failures that occur in the first cycle of the FDA review process slow time to approval, reduce investment returns and, in some cases, lead to drug withdrawals or suspensions at the process’s final stage. At Phase III, half of drugs fail to advance due to a measure of efficacy which may be due, in part, to poor trial design or communication issues between sponsors and regulators earlier in the process.<sup>33</sup> Communicating expectations using a more structured framework could help address and resolve safety, dosing, and data integrity issues prior to New Drug Application (NDA) submission, and result in greater overall pipeline productivity.

Through our research on stakeholder perspectives and interviews with experts on the drug development and approval process,<sup>i</sup> we have formulated assumptions about how each of the three priority areas may impact critical stages in the pipeline (Table 1).



i. We interviewed internal specialists from Deloitte’s life sciences and federal practices, as well as external experts including senior leaders from biopharma companies who are involved in the drug approval process and experts from policy think tanks and regulatory agencies.

**Table 1: Potential impact of priority area interventions on the drug development process**

Phase	Benefit-risk	Patient-reported outcomes (PRO)	Real-world evidence (RWE)
<b>Summary</b>	<ul style="list-style-type: none"> <li>Encouraging a more structured, transparent, quantitative framework (for example, the broader use of decision models like the EMA's) could reduce concerns about subjective drug assessments and, potentially, speed approvals.</li> <li>A transparent framework could also enable better manufacturer decision-making around the advancement of drugs in the pipeline.</li> </ul>	<ul style="list-style-type: none"> <li>Incorporating wide-spread use of PRO data could reduce the complexity of clinical trials and expedite patient recruitment.</li> </ul>	<ul style="list-style-type: none"> <li>RWE uptake could broaden interest in using adaptive pathways in clinical trials.</li> <li>RWE could accelerate changes to traditional evidence hierarchies (i.e., where RCTs are considered best data sources, followed by observational data, etc.), creating more diverse approval pathways for new indications.</li> </ul>
<b>Phase I entry and transition to Phase II</b>	<ul style="list-style-type: none"> <li>Transparency could help reduce early uncertainties about the end goal, encouraging more drugs to enter the Phase II pipeline.</li> <li>An aligned, enhanced framework could lead to better information to design Phase II trials and support patient recruitment.</li> </ul>	<ul style="list-style-type: none"> <li>PRO use could provide an early indication of patient experiences and preferences, which would support better-designed Phase II trials.<sup>34</sup></li> </ul>	<ul style="list-style-type: none"> <li>RWE may provide additional scientific information to inform Phase II design and patient recruitment.</li> <li>RWE might lead to earlier attrition by providing evidence that may signal a compound's low likelihood of success.</li> <li>RWE may increase the number of indications being pursued.</li> </ul>
<b>Phase II and transition to Phase III</b>	<ul style="list-style-type: none"> <li>Improved certainty about process requirements might encourage more sponsors to put greater investment into Phase III trials.</li> <li>Early signals to sponsors on safety requirements could help them improve data collection to demonstrate the drug's safety profile, a key reason for failure.</li> </ul>	<ul style="list-style-type: none"> <li>Better knowledge of patient parameters could enable expedited patient recruitment.</li> <li>Greater use of adaptive trial design and surrogate endpoints could expedite efficacy assessment.</li> <li>Combined, both impacts could result in cycle time reduction.</li> </ul>	<ul style="list-style-type: none"> <li>RWE may accelerate patient selection and enrollment and therefore increase initiation and investment in Phase III.</li> <li>Adaptive trial designs may reduce the number of protocol amendments.</li> <li>Using RWE in Phase II dose response assessments could improve Phase III dose selection.</li> <li>RWE may lead to investigation of narrower, more targeted indications.</li> </ul>
<b>Phase III and transition to application</b>	<ul style="list-style-type: none"> <li>A clearer benefit-risk process might inform better trial designs in Phase III.</li> <li>Greater patient involvement in benefit-risk models could make advancement easier and encourage more filings.</li> </ul>	<ul style="list-style-type: none"> <li>PRO data could serve as valid outcomes surrogates for Phase III drugs.</li> <li>Novel trial designs might speed NDA filings.</li> <li>PRO could help identify patient subsets which benefit from treatment and advance new indications.</li> </ul>	<ul style="list-style-type: none"> <li>RWE could improve identification of patients and genetic information to expedite Phase III trials.</li> <li>As RWE leads to investment focused in higher-value areas, more NDA filings may be possible.</li> <li>RWE could help in trial design – particularly the use of adaptive pathways – currently used on 20 percent of clinical trials, mainly in Phase III.<sup>35</sup></li> <li>RWE could provide data supporting NDAs and label expansion.</li> </ul>
<b>Approvals</b>	<ul style="list-style-type: none"> <li>A more quantitative benefit-risk process, and earlier and clear communication about safety risks, could improve consistency and efficiency of first-cycle approvals.</li> </ul>	<ul style="list-style-type: none"> <li>Greater use of PRO data might speed first-cycle approvals or any requirements for resubmission of data.</li> <li>PRO may make the approval process for subsequent indications faster and more likely.</li> </ul>	<ul style="list-style-type: none"> <li>RWE could help support a more robust submission package for the lead and supplemental indications.</li> </ul>

## Considerations

Our review primarily addresses factors that could reduce regulatory uncertainty and improve the quality and application of data being generated during the R&D process. However, factors such as the implementation of capabilities such as gathering new sources of data, shifting payer coverage policies, and ability to use potentially richer data to inform sponsor decision-making earlier in the development process could also influence the number and quality of compounds that make it to market. Among other considerations:

**Recognize the benefits of priority area interventions may take time.** If implemented, biopharma companies will need to possess a number of capabilities to realize the full benefits of the priority area interventions. These include the ability to tailor clinical protocols to quantitative benefit-risk frameworks; to design and validate PRO instruments; and to capture, evaluate, and incorporate RWE into pipeline decisions. The transition is likely to take time and dedicated investment.

**Evidence-driven strategies may aid decision-making at key stage gates.** Due to biopharma R&D's high cost and complexity, companies may choose to focus investments on compounds with a high probability of making it to market. The evidence-driven stakeholder priorities described above should help manufacturers generate more targeted, robust clinical data sets which, in turn, may enable better decision-making at key stage gates. For example, a transparent benefit-risk framework could allow biopharma companies to design clinical trials targeted at gathering data to assess defined outcomes measures. Also, incorporating PRO strategies could provide early-stage insights into patient preferences. All of this information would support strategic decisions about whether or not a drug is worth progressing to later stages or what development path a drug should take. As a result, there may be an increase in early-stage attrition, which could free-up resources, allow drug sponsors to make better capital and asset allocations and, perhaps, invest in therapy areas that could bolster a robust Phase III portfolio. For the drugs that a company does decide to pursue, a greater body of available evidence could help target drug development plans to specific subpopulations. As a result, the products that remain in the pipeline are likely to be of higher quality and, therefore, may increase the probability of later-stage success.

**Broader sources of evidence may result in more valuable products making it to market.** As US health care continues to shift its focus from volume-to-value, and payers and providers operate under increasing cost pressures, products that make it to market will likely need to demonstrate how clinically and economically differentiated they are if their sponsors hope to realize their full commercial value. Should the relevant stakeholders implement the three proposed priority area interventions outlined, biopharma companies should have richer data and evidence to assess how a product in development compares with competitive treatments and how it may benefit certain subpopulations. Such data may enable companies to focus investments on products that, when given to the right patient at the right time, have greater potential to improve outcomes. As a result, the value of compounds that make it to market is more likely to be higher, with greater potential to impact patient care.

## The path forward

Biopharma companies, regulators, and the research community will need to integrate new technologies and a huge and growing influx of data into the decision-making process. Increased stakeholder input and collaboration should help to ensure that this data is leveraged so that early laboratory findings can be translated into therapies that improve patients' health. The priority areas outlined in this paper have the potential to improve the efficiency of the drug pipeline, and to develop safe and effective treatment options for patients around the globe. We recognize that the path forward will not be easy. Industry and regulatory agencies may need to dedicate resources to advance their individual initiatives, and then identify opportunities to jointly define, communicate, and achieve shared goals.

Ultimately, it will be up to regulators to put forth consistent, aligned guidance around incorporating quantified benefit-risk frameworks, PRO, and RWE into the approval process. However, the biopharma industry should consider continuing its efforts to align on approaches that could achieve the same goal. The Biotechnology Innovation Organization (BIO) has recently published guidance for the industry on how to incorporate patient perspectives into the FDA's qualitative framework for benefit-risk assessment.<sup>36</sup> Additional progress can be made if stakeholders use established venues and coalitions to define frameworks and continue creating and implementing approaches across all three priority areas.

## Endnotes

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