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Therapeutic Innovation & Regulatory Science published online 29 October 2013
DOI: 10.1177/2168479013508941

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What is This?
Evolving Global Regulatory Science Through the Voluntary Submission of Data: A 2013 Assessment

Elizabeth Gribble Walker, PhD¹, Martha Brumfield, PhD¹, Carolyn Compton, MD, PhD², and Raymond Woosley, MD, PhD³

Abstract
Regulatory science, the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of regulated medical products, has advanced over time due to a number of factors. The FDA, the EMA, and the Pharmaceuticals and Medical Devices Agency (PMDA) have recently formalized voluntary data submission processes for the regulatory “qualification” of novel tools and methodologies for use in drug development. While recognizing that other mechanisms exist within the research community for driving scientific consensus on novel tools and methodologies, this article focuses on the formal regulatory process that addresses a tool’s acceptability for incorporation by any sponsor into novel medical product development. Guidelines, regulatory qualification opinions, and publications were reviewed to allow a systematic comparison of the process, content, and volume of submissions at the FDA, EMA, and PMDA. Qualification of new tools by regulatory agencies and subsequent adoption by drug developers are anticipated to speed therapeutic development for patients in need, build scientific consensus as to the usefulness and readiness of novel methodologies for understanding disease and therapeutic development, and decrease uncertainty between the regulators and sponsors regarding the appropriate application of new tools.

Keywords
regulatory science, biomarker, qualification, drug development tool, harmonization, novel methodology, critical path initiative, Critical Path Institute, Food and Drug Administration, European Medicines Agency, Pharmaceuticals and Medical Devices Agency

History of Voluntary Data Submission at the FDA, EMA, and PMDA
The relatively small number of new medicines approved to treat and cure disease over the last several decades is disproportionate to the billions of private and public dollars invested annually in biomedical research worldwide.¹ Improvements in the translational research process, that is, the developmental progression by which basic scientific discoveries are advanced to produce meaningful therapies for patients, are now considered critical to reversing this long-standing decline in return on investment in biomedical product development. Major funders of biomedical research are attempting to address this issue with initiatives such as the recent creation of the National Center for Translational Science (NCATS) and the Cures Acceleration Network (CAN) by the National Institutes of Health and the Innovative Medicines Initiative by the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA).²³ The increasing frequency and scope of research partnerships between pharmaceutical companies and academic labs represent additional examples of innovative approaches to address challenges in the current system.⁴ One essential, and sometimes overlooked, step in translational science is the drug review and approval process. The global regulatory agencies for new medical products are important stakeholders in the dialogue about—and necessary

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Submitted 19-Apr-2013; accepted 10-Sep-2013

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participants in the testing and implementation of—novel ways to advance translational science.

Roadblocks to getting effective new treatments to patients are numerous, but they are often the same for many disease areas. Often cited issues are lack of sufficient understanding of basic disease biology to identify drug targets; inability to identify the specific sub-population likely to respond to a drug in heterogeneous patient populations with similar clinical phenotypes; lack of consensus in what constitutes a clinically meaningful endpoint or how to appropriately measure an endpoint, including how to quantitatively assess a patient’s experience; lack of data standards to analyze results across multiple clinical trials; and safety concerns that dominate a benefit-risk scenario for patients.\(^5\)\(^-\)\(^9\) The traditional paradigm of confidential sponsor and regulator interactions around a particular development program provides limited opportunity for either developers or regulators to advance any of the aforementioned issues. Most academic investigators have very limited exposure to the singular perspective of regulatory thinking and are not practiced at the particular framing of research questions that could produce answers to increase the probability of a successful development program. No one laboratory, company, or even discipline is likely to solve these problems. However, the growing urgency and sense of a “broken” development paradigm are creating novel pathways to address these common roadblocks.

In 2003, the US Food and Drug Administration established the Voluntary Genomic Data Submissions (VGDS) process to enable sponsors to voluntarily submit and discuss genomic data in a confidential, mutual-learning environment that had no formal regulatory consequence. This was a new mechanism intended to aid any external party and the agency in determining the appropriate interpretation and application of genomic data to a particular program or disease area.\(^10\) The establishment of the VGDS process was a significant advance for the FDA, although lagging behind the widespread adoption of genomic technology by biomedical research and for internal use by industry. The need for a mechanism to discuss voluntarily submitted data, possibly divorced from a specific drug development program, with the agency was sufficiently appreciated, so the VGDS was expanded beyond genomic data to include data of any kind and rebranded as the Voluntary eXploratory Data Submissions (VXDS) process.\(^11\) With the rapid emergence of new biomedical technology today, the VXDS program provides a crucial mechanism for early exploration of applicability in the regulated environment.

While the VGDS was created with disconnection from regulatory action as implicit to its purpose, the desire for a mechanism to submit data important to the drug development process beyond the scope of a particular development program that could be coupled to a specific request for a regulatory action or acknowledgment soon became apparent. Many new technologies, methods, and biomarkers were described at length in the literature, and many companies had extensive internal experience with them. However, in the uncertainty of limited experience and not knowing how much data would be required for the FDA to accept these tools, sponsors were reluctant to utilize them in regulated nonclinical or clinical studies.

With the aim of developing a path to reach consensus on the appropriate application, or “context of use,” for a new tool and decrease inefficiencies in repeatedly evaluating data to support a tool on a case-by-case, program-by-program basis with sponsors, a pilot program was initiated in 2007 to explore and build upon the voluntary data submission process for a more formal “regulatory qualification” of drug development tools (DDTs).\(^12\) A simultaneous interest for such a process had been building in the EU and led to a joint and coordinated review between the FDA and the European Medicines Agency (EMA). The pilot qualification submission project was grown from a pre-existing cooperative research and development agreement (CRADA) between the FDA and Novartis, and it was augmented and submitted by the Critical Path Institute’s Predictive Safety Testing Consortium (C-Path’s PSTC). The pilot project analyzed an extensive dataset of nonclinical studies showing the utility of 7 biomarkers to detect nephrotoxicity in the rat in a more specific and sensitive manner than serum creatinine and blood urea nitrogen, the accepted methods for detecting nephrotoxicity.\(^13\) In 2008, the FDA and EMA publicly announced the first ever regulatory qualification of a novel tool or methodology for use in drug development.\(^14\),\(^15\) The Japanese Pharmaceuticals and Medical Devices Agency (PMDA) was an observer during this review and later formally performed their own independent qualification review, which was completed in 2010 and built upon an existing process for reviewing pharmacogenomics data.\(^16\)

Following this pilot project, the EMA published a new guidance, “Evaluation of Novel Methodologies for Use in Drug Development,” followed shortly after by the FDA’s “Draft Guidance for Industry: Drug Development Tool Qualification.”\(^17\),\(^18\) These guidelines define the intended outcome of the voluntary submission of data as a formal opinion regarding the utility of a novel DDT for a particular and well-circumscribed application in the drug development process, which is defined within a context of use. In 2009, the PMDA also established a pilot process for any sponsor to submit voluntary data supporting adoption of novel methodologies, which has recently been formalized.\(^19\)

The qualification process was created with a vision to provide a formal mechanism for the evaluation of novel DDTs, such as prognostic or predictive biomarkers, at the regulatory agencies to avoid redundant reviews on a case-by-case basis.
Similar advantages make up the value proposition for qualification for sponsors: increased efficiency in program design and decision making and decreased uncertainty as to utility and regulatory acceptance of “novel” tools. The voluntary submission of data through the qualification pathway holds promise to advance fields such as safety assessment, with adoption of more sensitive and specific biomarkers of toxicity, as well as improve clinical trial design through consensus on biomarkers for disease prognosis, patient population selection, and trial endpoints. Sponsors with development programs in a particular therapeutic area, patient research groups, academic investigators, and regulators are all stakeholders and beneficiaries of the successful consensus and adoption of novel tools with utility to improve decision making in the development of new therapies. Well-organized and administrated pre-competitive consortia with substantial provisions for protection of intellectual property, confidentiality, and data handling are likely vehicles for qualification.10,12

The Current DDT/Novel Methodology Qualification Process at the FDA, EMA, and PMDA

Although the qualification processes at the FDA, EMA, and PMDA are materially similar with a consultation phase and a review phase, several distinctions are important to note (Figure 1). For the purposes of this article, sponsor refers to a group of scientists, a consortium, and so on that is the submitter of data for qualification of a new tool—not to the sponsor of the development and marketing of a new medical product. Because the necessary body of evidence to support regulatory qualification of a new tool is so large and often extends beyond what is...
publicly available in the literature, or present within a single company’s knowledge base, sponsors of drug development/expert methodology programs are anticipated to most commonly be groups of vested stakeholders organized into pre-competitive consortia. Relevant factors for consideration by any potential sponsor are discussed in this section.

As previously mentioned, the EMA’s guidance was adopted in January 2009 and the FDA’s draft guidance released for public comment in October 2010, although a new version is anticipated in the near future (Table 1). The PMDA has undertaken a single pilot project—the translational qualification of nephrotoxicity biomarkers. In April 2012, the PMDA expanded the program by establishing new categories to provide more opportunities for a sponsor in the planning and review phases of qualification.

The length of time that the qualification process has been in place, the number and breadth of qualification applications considered and reviewed, the scope of regulatory responsibility for the agency, and the dedicated resources for qualification at each regulatory agency all contribute to the overall expediency, emphasis, and experience of the consultation and review process. A major difference between qualification at the FDA and EMA relates to the EMA’s fee for qualification advice and adoption of the pre-existing framework for scientific advice and opinion already in place at the agency. Fees for advice provide resources and commit the agency to specific timelines for expedient review at each stage of the process. For example, once a sponsor submits a letter of intent (LOI) and qualification draft dossier, the EMA will assemble its review team, review the dossier and meet internally to discuss, issue a list of questions, and hold a meeting with the sponsor within 120 days. Qualification review teams with the appropriate expertise for a particular application are drawn from the established EMA network of scientific experts under the auspices of the Scientific Advice Working Party (SAWP). The SAWP will review the qualification submission and make a recommendation to the Committee on Medicinal Products for Human Use (CHMP), which issues the final advice or opinion.

In contrast, the FDA has dedicated staff within the Office of Translational Science to provide scientific and administrative oversight of the Qualification Program and informal target review and response times. Prescription Drug User Fee Act (PDUFA) fees may assist with hiring more dedicated staff, but no specific allocation in PDUFA V has been designated for dedicated time for scientific staff within the review divisions, nor have timelines for qualification been mandated. Both agencies do structure their review into a consultation and advice phase (EMA: qualification advice) and a review phase (EMA: qualification opinion) following the submission of a LOI and a briefing package or dossier from the sponsor. Both agencies acknowledge the possibility that a dataset may be initially sufficient to proceed directly from LOI to the review phase of a qualification submission—as compared to consultation and advice following submission of a briefing document that would direct the completion of the research and data analysis—but this would likely be a rare scenario. The existence of compulsory timelines at the EMA means that qualification advice could be received as quickly as 120 days following submission of a LOI and briefing dossier and, potentially, a follow-up qualification opinion 100 days (not counting the public consultation period) after the sponsor incorporated the advice and submitted a full data package. Responsiveness of the sponsor to regulatory requests can also majorly contribute to overall timelines for the consultation and review phases at either agency. While fees at the EMA and PMDA are a significant consideration, the possibility of a relatively expedient review may be a worthwhile trade-off, especially for consortium projects where measurable progress and meeting milestones and goals are critical to enthusiastic participation.

Since the initiation of the qualification process at the FDA and EMA, a relatively high volume of inquiries and submissions have been received. At the writing of this article, the FDA has reported a total of 39 projects (25 clinical outcome assessment tools; 14 nonclinical and clinical biomarkers) currently in the consultation and advice phase (M. Walton and L. Burke, FDA, personal communication, September 10, 2012), although only 3 qualification submissions have progressed through the end of the review phase (Table 2). The EMA’s accounting for projects in the qualification advice or qualification opinion phase is somewhat distinct from the FDA’s; however, the agency confirmed that qualification advice has been finalized for 18 projects with 5 ongoing (5 clinical outcome assessment tools; 18 nonclinical and clinical biomarkers). These qualification advice procedures have dealt with myriad therapeutic areas including CNS (n = 11), nephrology (n = 3), gastroenterology (n = 2), oncology (n = 2), pulmonary (n = 3), cardiology (n = 1), and musculoskeletal disorders (n = 1) as shown in Table 2 (S. Vamvakas, EMA, personal communication, August 24, 2012). Completed qualification submissions at the FDA (n = 3) and EMA (n = 6) have been dominated by biomarkers for proposed use in nonclinical safety assessment and for clinical trial enrichment in Alzheimer’s disease (Table 3). This is a combined phenomenon of public health need and specific timing and interests of the sponsors on these projects, including those of 3 large, pre-competitive consortia.

The context of use for the DDT that is proposed for qualification is the central concept refined throughout the consultation phases with the regulators. The health authorities emphasize qualifying a concise, yet highly prescriptive description of exactly how a qualified biomarker may be applied by any sponsor on a future development program, somewhat akin to the language agreed upon for the label of a newly approved drug. The context of use for a qualified biomarker indicates exactly...
<table>
<thead>
<tr>
<th></th>
<th>FDA</th>
<th>EMA</th>
<th>PMDA</th>
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</thead>
<tbody>
<tr>
<td>Review team</td>
<td>Biomarker Qualification Review Team (BQRT): composed of staff from therapeutic divisions at CDER. Chaired by 1 individual.</td>
<td>Qualification Team: Appointed by CHMP, led by coordinator, composed from EMA experts’ network</td>
<td>Qualification Review Team, PMDA Omics Project Team (POPT): composed of experts from various divisions (eg, new drug, Good Clinical Practice, device) at PMDA. Will use external experts if appropriate.</td>
</tr>
<tr>
<td>Public consultation period?</td>
<td>No</td>
<td>Yes for qualification opinion. EMA qualification report posted for public comment prior to final opinion.</td>
<td>No</td>
</tr>
<tr>
<td>Scope of acceptable biomarker requests</td>
<td>Any drug development tool for clinical or nonclinical context of use including imaging but NOT drug/diagnostic co-development. The Center for Devices and Radiological Health handles approval of devices.</td>
<td>Innovative drug development methods and tools for clinical or nonclinical context of use including imaging</td>
<td>Any biomarker for clinical or nonclinical context of use including imaging but NOT an individual drug/ diagnostic development program</td>
</tr>
<tr>
<td>Fee¹</td>
<td>None</td>
<td>77,900 Euros (approx. US$94,721) for initial advice or opinion; 38,900 Euros (approx. US$47,299) for follow-up advice or opinion</td>
<td>3,030,000 Yen (approx. US$38,775)</td>
</tr>
<tr>
<td>Regulatory product</td>
<td>Formal regulatory opinion issued in form of drug development tool qualification recommendations and supporting documentation will be made publicly available on FDA website with notice of availability published in federal register.</td>
<td>Formal CHMP Qualification Opinion issued in form of letter to sponsor and EMA-drafted report made publicly available on EMA website.</td>
<td>Formal qualification opinion issued in form of letter to sponsor and PMDA-drafted report containing overall summary from sponsor made publicly available on PMDA website.</td>
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</table>

¹ Subject to annual adjustment and posted publicly. European small and medium sized enterprises (SMEs) eligible for 90% fee reduction with the EMA. For biomarkers intended for use in orphan diseases, the EMA may grant a 75% fee reduction for any applicant and a 100% fee waiver for SMEs.
how the data submitted by the sponsor support its application. For example, low hippocampal volume quantified by volumetric magnetic resonance imaging (MRI) was qualified by the EMA as a biomarker for clinical trial enrichment to select patients with mild cognitive impairment (MCI) likely to progress to Alzheimer's disease (AD) within 24 months in trials for drugs aimed at slowing or halting the progression of AD. Hippocampal volume, and/or other biomarkers currently qualified for clinical trial enrichment, may also have diagnostic utility but have not been qualified at that capacity at this time. Table 3 lists the qualified context of use for all biomarkers with a published regulatory opinion on their utility. For brevity, these have been paraphrased as needed; the reader is referred to the source regulatory document for exact details.

The regulatory mandate of each agency contributes to the particular discussion of context of use. Because the FDA and PMDA have divisions responsible for the regulatory approval of medical devices, including diagnostic tests, these agencies may more specifically emphasize the measurement science utilized in the acquisition of data in the qualification package. Considering the extensive data generated and reviewed by the regulatory agencies during the qualification process, these new DDTs may open an opportunity for interested device developers to actively partner with sponsors during qualification or pursue device registration post-qualification.

### Assessing Success and the Impact of Qualification on Drug Development

For regulatory qualification to be successful and achieve longevity, both regulators and potential DDT sponsors must perceive positive impact on the drug development process, that is, return on investment. Qualification is resource intensive, and its proponents and stakeholders should appropriately assess the cost-benefit results. Two questions related to assessing the impact of qualification should be addressed. First, is regulatory qualification an effective mechanism for improving regulatory science, that is, promoting the adoption of new tools for assessing drug safety, efficacy, quality, and performance? And second, how impactful are those new tools in their intended application, for example, advancing efficacious therapeutics for patients or promoting the development of drugs with fewer or better defined toxicities?

Due to the prolonged nature of the drug development path from discovery to post-marketing, the relative newness of the qualification program, and the limited numbers of DDTs that have been qualified thus far, it may be exceedingly difficult to answer the latter question at this point. Despite costing more per biomarker assay than serum creatinine and blood urea nitrogen, the kidney safety biomarkers currently qualified for nonclinical use are anticipated to enable more informed and rapid decision making in evaluating benefit-risk of a compound with possible nephrotoxicity, leading to increased efficiencies and reduced cost for a nonclinical development program overall. The imaging and cerebrospinal fluid (CSF) biomarkers qualified for clinical trial enrichment in AD should enable more accurate identification of patients with mild cognitive impairment who are highly likely to progress to AD. Using these biomarkers to select a clinical trial population should result in fewer subjects needed for a trial of shorter duration and simultaneously increase the probability to detect a therapeutic effect while decreasing trial cost. Moreover, patients with episodic memory loss not due to AD would be spared from clinical trials for which they are inappropriate candidates. Additional metrics for measuring the success of a qualified DDT might include several assessments of increased efficiency in drug development: faster decision making for advancing or terminating developmental compounds, increased numbers of compounds progressing through the pipeline, and reduced cost of nonclinical and clinical development programs.

Ultimately, impact to patients in the intended therapeutic area can be estimated, but the cumulative time from DDT qualification to DDT implementation for developmental compounds to new drug approval to measuring patient benefit is likely a minimum of 5 to 7 years. The rate of adoption of a newly qualified tool by developers can be anticipated to increase as the regulatory qualification process gains more familiarity. However, although participants in a qualification submission are ideally representative and inclusive of vested stakeholders, this may not always be the case, and those entities closest to the data generation and analysis in support of a qualified DDT will always be more rapid adopters than
### Table 3. Currently qualified biomarkers at FDA, EMA, and PMDA.

<table>
<thead>
<tr>
<th>Drug Development Tool</th>
<th>Context of Use</th>
<th>Health Authorities Where Qualified</th>
<th>Qualification Sponsor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary renal biomarkers (Kim-1, albumin, total protein, B-2 microglobulin, cystatin C, clusterin, trefoil factor-3)</td>
<td>NONCLINICAL: Biomarkers are acceptable for voluntary use in nonclinical drug development for the detection of acute drug-induced nephrotoxicity, either tubular or glomerular with associated tubular involvement. They provide additional and complementary information to blood urea nitrogen (BUN) and serum creatinine to correlate with histopathological alterations. CLINICAL: The use of these renal biomarkers in clinical trials may be considered on a case-by-case basis in order to gather further data to qualify their usefulness in monitoring drug-induced renal toxicity in humans.</td>
<td>FDA, EMA, PMDA</td>
<td>Critical Path Institute’s Predictive Safety Testing Consortium</td>
<td>14, 15, 16, 23</td>
</tr>
<tr>
<td>Urinary renal biomarkers (clusterin, RPA-1, α-GST [EMA only])</td>
<td>Urinary clusterin is a biomarker that may be used by applicants to detect acute drug-induced renal tubule alterations, particularly when regeneration is present, in male rats and can be included along with traditional clinical chemistry markers and histopathology in good laboratory practice (GLP) toxicology studies that are used to support renal safety in clinical trials. RPA-1 is qualified for the same context of use as stated above but is specific to the collecting duct in the kidney. EMA only: The data may support the use of urinary α-GST in detecting proximal tubule injury in male rats.</td>
<td>FDA, EMA</td>
<td>Health and Environmental Science Institute’s Committee on Biomarkers of Nephrotoxicity</td>
<td>24, 25, 26</td>
</tr>
<tr>
<td>Cerebrospinal fluid (CSF) biomarkers for Alzheimer’s disease (Aβ1-42, total tau, phosphorylated tau)</td>
<td>In patients with MCI as evaluated by Dubois criteria, a positive CSF biomarker signature based on a low Aβ1-42 and a high T-tau can help predict evolution to AD dementia type and is useful for clinical trial enrichment for drugs affecting amyloid burden in Alzheimer’s disease.</td>
<td>EMA</td>
<td>Bristol-Myers Squibb</td>
<td>27</td>
</tr>
<tr>
<td>Volumetric imaging of hippocampal volume for Alzheimer’s disease</td>
<td>Low hippocampal volume (HV), as measured by MRI and considered as a dichotomized variable (low volume or not), may be used along with clinical criteria to help enrich recruitment into clinical trials aimed at studying drugs potentially slowing the progress/conversion to AD dementia. Low HV might be considered a marker of progression to dementia in subjects with cognitive deficit compatible with predementia stage of AD (Dubois, 2007), for the purposes of enriching a clinical trial population. However, neither the actual value of low HV to accurately predict the rate of such progression in the referred subjects nor the relative value of other biomarkers has been reported.</td>
<td>EMA</td>
<td>Critical Path Institute’s Coalition Against Major Disease</td>
<td>28</td>
</tr>
<tr>
<td>Positron emission tomography (PET) amyloid imaging in Alzheimer’s disease</td>
<td>Amyloid related positive/negative PET signal qualifies to identify patients with clinical diagnosis of predementia AD who are at increased risk to have an underlying AD neuropathology for the purposes of enriching a clinical trial population. However, neither the actual value of PET (+) or (–) to accurately predict rate of such progression to dementia in the referred subjects nor the relative value of other biomarkers has been reported. Thus, we recommended to follow-up these patients until clinical diagnosis of mild AD is made.</td>
<td>EMA</td>
<td>Bristol-Myers Squibb</td>
<td>29</td>
</tr>
<tr>
<td>Circulating cardiac troponins T and I</td>
<td>Serum/plasma cardiac troponin T and I are biomarkers of cardiac morphological damage and are useful for specific purposes in nonclinical safety assessment.</td>
<td>FDA</td>
<td>O’Brien, Reagan, York, and Jacobsen</td>
<td>30</td>
</tr>
</tbody>
</table>

Some context of use (COU) statements have been paraphrased as needed for brevity. In some instances where a DDT submission was reviewed by multiple agencies, the qualified COU differs slightly (e.g., ILSI/HESI nephrotoxicity biomarkers, FDA and EMA, 2010). The approved full COU is available online from each agency.
companies less familiar with the DDT. Although qualification may ultimately speed the development of medicines for patients in need, this goal may take considerable time to realize. As the qualification process matures and itself becomes more efficient, and as greater numbers of qualified DDTs become available to the community, the impact would be expected to crescendo.

A second challenge to assessing impact of qualified DDTs is the potential unwillingness of developers to be meaningfully transparent about how qualified DDTs are applied to internal development programs. Although qualification of the DDT may be performed in pre-competitive space, actual adoption may be perceived to provide competitive advantage. Although contributing data toward qualification of more sensitive and specific safety biomarkers to assess and progress safer compounds and enable more careful patient safety monitoring is arguably an ethical mandate for drug companies, companies may be more reluctant to share exactly how those biomarkers are strategically applied at different stages to support specific decisions that advance a particular therapeutic program. Additionally, if a company can fill critical data gaps to more fully expand a context of use of a DDT that provides timely and specific competitive advantage to their developmental program, it is difficult to conceive that this information would be made publicly available until the advantage were exploited. Thus, the prioritization, funding, and critical data sources for qualification projects must be carefully planned by all stakeholders— regulators, developers, patient research groups, disease foundations, and possibly payors as well.

The perception of moving back into competitive space when the qualified DDT is applied to a developmental program also hinders the ability to track the uptake of qualified DDTs by developers. Post-qualification, the sponsor is not incentivized to divulge that it is using the new DDT, and the regulator is prohibited by confidentiality provisions. However, for the sustainability of the qualification process, it is imperative for those who help coordinate and fund qualification projects to be able to speak of their successes, beginning simply with the number of applications where a DDT is applied. A database for tracking when and, ideally, how qualified DDTs are used in development programs is most feasibly mandated by or implemented at the regulatory agency level, where a comprehensive scan of all active programs as well as de-identification of sponsors, if desired, is possible, albeit expensive and complex. The online clinical trial registry clinicaltrials.gov may ultimately capture some qualified DDTs in use; however, none of the current FDA-qualified tools would be recorded as they relate exclusively to nonclinical safety biomarkers. While even qualified clinical safety biomarkers are highly unlikely to be recorded here, this registry may be useful for tracking some DDTs used as primary endpoints or inclusion criteria for a trial. Because reporting for clinicaltrials.gov is required for only a portion of total global trials, that is, those involving an FDA-regulated drug, biological product, or device with a trial or manufacturing site in the US or conducted under an FDA investigational new drug application, it would not wholly track qualified DDT use.

In addition to providing useful information for tracking whether regulatory qualification speeds adoption of novel tools, a purpose-built central database would ultimately help promote community learning regarding the DDT. This includes the internal dissemination of educational information at a regulatory agency to ensure that the DDT is being appropriately and consistently recommended for use across review divisions, as well as the iterative and ongoing refinement of the context of use for a DDT. Presumably, the science supporting the utility of a DDT will continue to grow, and the context of use must evolve accordingly.

The Sustainable Future of Qualification

Who should assume responsibility for the ongoing maintenance of a qualified DDT? A submission is made for an initial and often restricted context of use with the anticipation that it will expand and evolve as the evidence is generated to support further applications, including combinatorial approaches with additional biomarkers. This evolution of a DDT’s context of use should continue into perpetuity, including the realistic and eventual extinction of the DDT as it is replaced by an entirely new tool. Currently, qualified DDTs at the FDA, EMA, and PMDA have been sponsored by a drug company, a group of expert investigators, and a small number of pre-competitive consortia (Table 3). It is interesting that each of these types of sponsors has a compelling value proposition for submitting and maintaining the DDT, and yet the sustainability in motivation and resources for doing so is not necessarily guaranteed for any of these.

Review of the EMA qualification opinions of the CSF and imaging biomarkers for AD clinical trial enrichment makes clear that the agency is eager to understand how these biomarkers directly compare with each other, and whether combinations of the biomarkers improve identification of patients with MCI or predementia with a high probability to develop AD. The EMA cannot compel the qualification sponsors to cooperate with one another, nor to reveal the data (if it exists) to make these biomarker comparisons. However, at minimum, the regulatory agencies may use their influence and interest in specific research questions related to DDTs to highlight topics of public health utility to funding sources, including pharmaceutical companies. If qualification projects accurately address high impact areas, confirming cost-effectiveness of applying these novel DDTs should incentivize drug developers to invest
in further understanding of the tool’s utility. An independent, third-party consortium is an obvious vehicle for DDT development and maintenance as participation is likely to be open to diverse sources of expertise, resources, and data, including those from drug companies. However, an ongoing incentive for cooperation and public learning will need to be present, as well as a sustainable source of funding to support the consortium infrastructure and the project budget. The DDT qualification process is envisioned to greatly aid the regulatory agencies in achieving their mandate; accordingly, they may play a pivotal role in enabling ongoing learning regarding a DDT. This could specifically involve the development of a publicly accessible database of DDTs and providing funding to public-private partners to coordinate DDT development programs with provisions for maintenance and promoting the assessment of DDT impact on drug development.

Qualification was piloted and implemented in parallel at the FDA and EMA and very recently formalized at the Japanese PMDA. Regulatory qualification is a process conducive to harmonization, as all 3 agencies appear to fundamentally agree on most of the necessary procedural steps and the basic format of data submissions. The ICH agencies have indicated willingness to collaborate with each other to establish internationally qualified biomarkers that are appropriate in the era of global drug development. Through existing agreements, ICH agencies do share and discuss qualification submissions that are jointly submitted. However, a truly streamlined consultation and review process remains an aspirational goal. Beyond the ICH, other regulatory bodies have expressed interest in regulatory qualification of novel DDTs. Although only a few years old, there are sufficient insights from submitters to the FDA and EMA to emphasize some recommended best practices that might guide regulatory entities seeking to establish regulatory qualification. Global interest by these health authorities signals perceived promise in this mechanism for voluntary data submissions.

The full potential for streamlined, global assessment and adoption of novel tools into regulatory decision making in drug development is exciting to visualize, but can it be achieved? For sustainable expansion at the FDA, EMA, and PMDA, as well as to additional agencies, the scientific community must conclude that qualification is a valuable investment in keeping regulatory science apace with biomedical advances. We cannot yet determine if qualification is an essential pathway for driving translational science to deliver medicines to patients in need, given the limited number of FDA-, PMDA-, and EMA-qualified tools (n = 6 unique submissions; Tables 2 and 3). Further analysis is critically needed to assess whether qualification leads to more rapid adoption by developers, successful outcomes for drug development programs, and ultimately, patient benefit. Over the next several years, it is hoped that the nearly 50 projects cited by the FDA and EMA as having received consultation advice (Table 2) will advance to full regulatory qualification. A basic framework for tracking and assessing success of those novel tools should be rapidly developed and implemented to elucidate the value of voluntary submission of data for regulatory qualification.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
Partial funding for this work came from grants from Science Foundation Arizona (SRG 0335-08) and the US Food and Drug Administration (5U01 FD003865).

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