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Subcommittee on Health Hearing On

"21st Century Cures: Modernizing Clinical Trials"

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Good morning, Chairman Pitts and Ranking Member Pallone, and members of the Health Subcommittee; thank you for the opportunity to appear before you today and to add to the 21st Century Cures Conversation.

My name is Paula Brown Stafford; I am President of Clinical Development at Quintiles, the world's largest provider of biopharmaceutical development and commercialization services, with more than 29,000 employees globally, including nearly 10,000 in the U.S. Together we deliver services in over 100 countries and are engaged every day in helping bring better medicines to patients faster. To give you a sense of our scope, over the past 10 years, we have enrolled nearly 1M patients in clinical trials at over 100,000 investigative sites. We are pleased to be part of today's hearing on Modernizing Clinical Trials.

The breadth and depth of our experience, as well as our role as a facilitator of the process, gives us a unique vantage point on where the challenges - and opportunities - are in the drug development process. It is a process we all agree is too expensive (in excess of $1 billion) and that takes too long – generally seven to 10 years. At the end, as we all know – patients are waiting.

Modernizing clinical trials is critical if we are to meet the goals we share of delivering better medicines faster, at less cost, to patients who need them. The biopharma industry and its service providers, along with FDA and other stakeholders have made great strides in improving the process. We work closely with our customers and the FDA to find better ways to design and execute studies to meet this goal, and have had many successes and appreciate the spirit of collaboration from the FDA. Nonetheless, more can be done.

My oral testimony will focus on three areas for further innovation and then offer a few of the suggestions of where Congress could help accelerate meaningful improvements.

1. Utilizing newer design approaches and improving data accessibility to improve our focus on **patients**, creating better ways to find the right patients for the right clinical trials;
2. Modernizing the **processes** of drug development, including ways to improve the quality and efficiency of clinical trials, reducing the timeline for each trial by eliminating redundancies and inefficiencies
3. Establishing alternative development **pathways** to speed the introduction of new therapies to address unmet medical needs.

In this written testimony, we provide a more comprehensive exploration of these areas, provide the rationale for solutions and make additional recommendations.

<u>Master Protocols and Adaptive Designs to Target Therapies to the Right Patients, Efficiently</u>

<u>The Challenge</u>

Clinical trial productivity is dramatically reduced and costs are vastly increased by the need for each Sponsor to conduct separate development programs in the same patient population for the same indications, for similar molecules or for molecules with common pharmacological mechanisms of action.

Drug development failure rates are high, time is wasted with duplicative recruitment and other efforts, and patient participation is not optimized.

A Solution

Various study design approaches that identify failures faster and advance promising drugs are available, including Adaptive Designs and Master Protocols.

Adaptive Trial Design: There are many types of adaptive designs, but all such designs use Bayesian methodology to characterize drug efficacy more precisely and efficiently in selected populations, based upon cumulative experience. It is also possible to combine adaptive design within Master Protocols, such that multiple drugs can be simultaneously evaluated, such drugs "rolling in" or "rolling off" as available for study and as evaluation is completed. This approach is currently being evaluated for wider adoption by the EMA. The national regulatory authority in Singapore has similarly investigated the use of adaptive authorization within Master Protocols.

Master Protocols: A Master Protocol allows multiple drugs to be evaluated in the same trial, with inclusion criteria that are relatively homogenous, and any necessary customization based on drug characteristics. Multiple compounds for a particular indication can be tested within the same Master Protocol, rather than requiring a separate protocol/development program for each. Only one placebo-controlled arm would be required instead of duplicating the same arm for each drug. This standardized, progressive regulatory approach would require fewer patients be on placebo and fewer enrolled overall, and significantly reduce costs and timelines by not requiring separate start-up and recruitment processes for different therapies.

The I-SPY 2 trial is an example of an adaptive trial using a Master Protocol, being carried out by a consortium involving industry and academia, with the collaboration of the FDA. I-SPY 2 takes an agile

approach, using a Master Protocol in which multiple oncology agents are evaluated in similar populations, with predefined success criteria, using a Bayesian adaptive design. The trial is for women with newly diagnosed locally advanced breast cancer segregated into treatment arms based upon biomarkers and other criteria. The study is evaluating whether adding investigational drugs to standard chemotherapy is better than standard chemotherapy alone before having surgery, using complete radiographic response/remission, rather than event-free survival as the efficacy endpoint. The trial is simultaneously testing multiple investigational drugs thought to target the biology of each participant's tumor. If the data is supportive that a particular drug is may prove effective in a given patient subpopulation, this "proof of concept" study can form the basis for a subsequent Phase III trial, in which confirmation of response on this same radiographic endpoint can form the statutory basis for approval. The Sponsor must, however, commit to continuing the trial in order to assess the effects of the drug on event-free survival and to obtain broader labelling claims. Dr. King Jolly, Senior VP of Quintiles, serves as a member of the Executive Steering Committee of this trial, and has helped formulate operational, scientific, and regulatory strategies related to this program. Quintiles is also providing the traditional Clinical Research Organization (CRO) services for this trial, and has provided financial support.

Recommended Approach

Quintiles recommends encouraging the use of adaptive designs and Master Protocols to maximize identification of drugs that work in the patient population without having to duplicate efforts across multiple Sponsors. Congress could consider requiring a certain percentage (perhaps 10%) of therapies entering Phase II to include Master Protocols and adaptive designs and that regulatory standards and approval criteria be clarified to encourage multiple biopharma companies to collaborate on Master Protocols with Bayesian designs.

Using Data to Facilitate Better Clinical Trials and to Benefit Patients

The Challenge

The practice of medicine and evaluation of therapies is a continual process that has largely been an experience- and paper-based endeavour. Today's technologies offer greater opportunities to harness real-world data and perform advanced analytics to inform better medical decisions, identify new uses and cures, improve drug development timelines and success rates, and more. While there are many efforts and advances, more can be done to truly harness this value.

As the 21st Century Cures white paper points out, analyzing data from the delivery setting could improve Discovery, Development and Delivery of better treatments. Below are examples of the benefits of data analytics across the spectrum. Each of these is conducted today in varying degrees, but the accuracy and power of the insights are only as good as the data available for analysis:

Real World Data Drives Discovery	**Real World Data Improves Development**	**Real World Data Improves Delivery Decisions**
Improve understanding of disease and inform the next generation of development by identifying unmet needs and opportunities	Inform better study design, dosing, inclusion/exclusion criteria	Discover potential safety and interaction issues of approved therapies (which supports more aggressive approvals)
Identify new uses of approved therapies and support product extensions	Accelerate trial execution through integration with EMRs, with collection of data at point of care	Continually assess benefits and risks to inform better coverage and medical care decisions that reward value (cost *and* effectiveness)
	Accelerate patient recruitment through EMRs, social media, and internet-enabled patient portals that facilitate more rapid identification of patients suitable for clinical trials.	

A Solution

To achieve these benefits, public and private entities alike must continue to enable the evolution of clinical trial design and conduct from the traditional "analog and local" model to a "digital and global" one. This includes continued investment in technologies, expedited validation and use of new tools, and importantly, improved collection and accessibility of data.

In the **analog and local model** that is largely still the norm today, design and planning are based on individual experience, with patient recruitment depending on individual relationships. Finding the right patient is rather a hit and miss affair. Clinical trials are conducted with separate paper report forms that require duplicate entry of each visit (data in the clinician's usual patient care notes and then in clinical trial records) and rigid schedules. Before the adoption of electronic databases and analytics, interim data were not available for months at a time, and with conclusions drawn after biostatisticians combed through spreadsheets. Safety is demonstrated only through a large number of patients enrolled in studies. Clinical development programs are determined based upon regulatory precedent, the guidance from Key Opinion Leaders, and the experience of treating physicians.

In contrast, in a **digital, global model**, which the industry is making some small strides toward, design is informed by real-world large, de-identified datasets and performance and productivity metrics, with patient recruitment taking advantage of the Internet and social media. The right patient would be identified by prescreening through data collection instruments served through the Internet, and trials would be conducted by collecting data directly from EMRs or through data collected at point of care that is integrated with EMRs. Data would then be housed within HIPAA-compliant e-Source archives, accessible for real-time access, remote monitoring, and application of signal detection analytics to allow

"just-in-time" assessment of safety and protocol compliance. Interim data would be available within hours, and safety demonstrated through immediate access to real-world data. Clinical development, in effect, would be EMR-enabled.

Recommended Approach

To maximize benefits of technology and analytics to further public health there are varying steps Congress could take to improve the quality and accessibility of data, listed below in order from ideal to step-wise improvements:

Create a central repository of accessible securely de-identified patient-level data and make available for research use through appropriate licensing. This would speed discoveries and development and improve assessment of real-world safety in larger populations. It would be a bold step, but others – such as the UK National Health Service – have made this a public health priority, and are gaining benefits from data that have been adequately anonymized and 'de-risked.' Currently, there are many large stores of patient data that can be de-identified, but the risk of being associated with, or liable for, the re-identification of individual patients hampers the willingness of care networks to share data with external researchers and causes reluctance among sponsors to work with third parties to tap the data. There is a need for a source of de-identified patient data to allow outcomes to be tracked, allowing use of real-world post-marketing data to answer regulatory approval questions. Regulatory changes could be made to provide a safe harbor for use of de-identified real-world patient data.

Other steps that could lead to improvements, short of the central repository described above, include:

Unique Patient Identifiers: Unique, HIPAA-compliant patient identifiers that follow individuals across settings, care networks, multiple EMR and health information systems would enable more accurate and comprehensive tracking of treatment outcomes and disease prevalence, which would help post-

marketing surveillance, inform treatment options, identify treatment gaps and provide information to improve new drug development and clinical trial design and recruitment. At present, patient records and outcomes data may appear in many different places – including records from hospitals, pharmacies, ambulatory care centers, and death certificates – making accurate assessment of outcomes unattainable. A unique patient identifier would allow for easy decoupling of patients' identities and their record, protect privacy and reduce the disjointed nature of current systems and the duplication of identifying and de-identifying data as it is cleaned for research use.

Integration of EMRs: All EMR systems in the U.S. should ideally be interoperable to allow a free flow of longitudinal health data accessible by everyone. This would allow real-world outcomes to be discerned much more quickly, allowing risk/benefit assessment to be carried out on millions of patients in near real time. This would transform the way we do clinical trials, giving access to patient data from all sources – doctor's office, urgent care, pharmacy clinics, hospitals, secondary, tertiary care centers – allowing complete tracking of patient care and outcomes. The Partnership to Advance Clinical electronic Research (PACeR) initiative[1] is aiming to standardize data across multiple EMR systems, and to implement clinical trial data collection systems that "wrap around" EMRs, allowing continuity of care across all locations. CDISC has an initiative underway in this area and is a member of PACeR. The government of Singapore has a mostly-uniform, countrywide uniform EMR system with a lot of interoperability, allowing comprehensive assessment of safety data and outcomes. This has given the regulatory authorities the confidence needed to approve products for narrowly defined populations from smaller trials, followed by additional, larger trials to expand the label (adaptive or staggered licensing/approval).

[1] http://pacerhealth.org

Improved Data Standards/Integration to unlock the power of real-world late phase data: Improved data standardization and integration is needed, as is the ability to contact patients directly via digital communities. There is scope for standardization of Electronic Data Capture (EDC) formats, which at present are different in each company. Standards should be established for data that are gathered iteratively and are common to every trial, such as safety, demographics, pharmacokinetics and clinical pharmacology, and in some cases, therapeutic standards. EMRs are most useful in integrated delivery systems. In the U.S., there are many different EMR vendors/systems, and they are used in various permutations. For the most part, such systems are not interchangeable; nor are they configured for clinical trials. Quintiles has put together the COMPASS Distributed Data Network[2] of around 10 EMR systems covering 19 million people for studies, and this is proving useful for safety and outcomes research. Another useful approach is to carry out hybrid studies using de-identified data from EMRs, supplemented by more focused data collection the physician and the patient. This approach allows better clinical trial functionality from EMRs. Safety and adverse event (AE) reporting could be stimulated using an add-on patch to the EMR, giving the physician the option to report that a symptom may be related to a drug; if yes, a link could pop up to MedWatch.

Use of Social Media and the Internet in Drug Development: Social media has changed the doctor-patient relationship and is fuelling the rise of patient empowerment. Online communities for sharing of information about disease symptoms, medication side-effects and clinical outcomes have become commonplace. Many entrepreneurs and established companies – and the government – are leveraging these networks to inform their development strategies, and even to identify and recruit patients. For example, Quintiles' Mediguard.org and ClinicalResearch.com support a community of patients who have opted to provide medication and condition information and are motivated to participate in research.

[2] http://www.quintiles.com/assets/0/111/118/233/1338/d098e5fb-d882-475d-b305-8865c2131aae.pdf

Currently, over 2.6 million patients in the U.S., UK, France, Germany, Spain, and Australia have registered making it one of the largest and fastest-growing healthcare communities in history. Social media-based interactions of this kind represent a disruptive technology that can harness large, de-identified datasets. There is potential for a new research paradigm for data collection, adverse event reporting and even direct-to-patient recruiting for clinical trials, and social-media based trials. Potential benefits for clinical trials are far-reaching, including lower cost and high speed versus traditional site-centric model, better connectivity between multiple healthcare stakeholders, reduction of geographical limits, and the potential for long-term contact and participation.

Looking ahead, social media could accelerate timelines and reduce the costs of drug development in some diseases, with the potential to contact motivated patients directly, rather than working through the complexities and expenses of site contracting. The advent of a social media based trial is not unthinkable, and this is a truly disruptive force in healthcare. As with traditional trials, though, high data quality will be essential. The policy issue for today is to ensure adequate data protection and patient safety – including provisions for informed consent – without 'handcuffing' patients' ability to 'opt in' to research in the public forum of the Internet. Congress needs to protect such clinical trial participants from discrimination or other harms based on what they reveal online. The fact that pre-existing condition exclusions for health insurance are now prohibited is a step in the right direction.

Sharing of Precompetitive Data: It would be helpful if precompetitive data of no direct commercial value – including placebo data, safety and other data, data related to products that have failed and are no longer being developed, and data on products that are off patent – could be made available for modelling and simulation of trial outcomes. This could improve the probability of trial success for all

Sponsors. For example, under the new openFDA initiative the FDA is making public millions of reports about prescription medicines, such as adverse events and medication errors, between 2004 and 2013. The FDA has also done some work to encourage companies to submit genomic data associated with their early development programs to add to the general body of knowledge. More data would allow validation of additional tools.

Each of these approaches would help in varying degrees to improve the quality and availability of data, and would in turn improve discovery, development and delivery of new cures and improved treatments for patients. With the data and analytical tools available today, we already see the value in terms of improving design, predictability and achievement of patient enrolment and ultimately improving probability of success. In the post-marketing phase, as data and techniques improve, there is tremendous potential for insights to improve care, identify new uses and assure safety. Congress should work to encourage the integration and accessibility of data, within the bounds of patient privacy.

Improving the Processes of Drug Development

Reducing Today's Clinical Trial Timelines

The Challenge

It is well documented that clinical trials are taking longer, and are becoming more complex and thus more expensive. The entire site start-up process, from Ethics Committee/Institutional Review Board (IRB) approval through site contracting can take up to 18 months. This must be completed before recruitment may begin. Ethics Committee approvals are a major delaying factor in clinical trial start-up; it can take up to a year to get approval to use a site, such as a hospital or medical practice. At present, for a 200-site study, the protocol is typically reviewed 200 times (once by each site) and 200 contracts are separately negotiated. The fastest timelines Quintiles typically sees for centralized IRBs are 45 days

to approval vs. 105 days each with local, individual IRBs. Other factors delaying start up include not enough standardized clinical trial documentation, which leads to 'reinventing the wheel' for each study and often each site and the fact that there is currently much duplication of effort in regulatory filings, and sometimes trial criteria, between the United States and the EU.

Solutions

Below are short-term pragmatic solutions that would help improve trial timelines and reduce unnecessary duplication of effort and thus cost:

Centralized Ethics Committee Approvals: Our experience shows that central IRBs, whose job is to perform this function, are two to three times faster at providing protocol review and approval to proceed.

Recommended Approach**:** Congress should urge the FDA to strongly encourage the use of central IRBs for the initial protocol review at the IND (investigational new drug) approval meeting – so that once a protocol has been approved by a recognized central IRB, it would effectively be approved for any site in the United States. Subsequent reviews at the site level IRB would focus on the specific requirements of each individual site (local regulations, and factors related to patients and investigators), but would not revisit the protocol and hold up the initiation of the other activities needed to get the trial up and running. Centralized IRBs are already used successfully in Europe, and a centralized process has also been implemented in hospitals in Quebec, including templates for informed consent paperwork.

Standardization of Clinical Trial Data and Documentation Requirements: Standardizing clinical trial data and documentation requirements, including qualifications for sites and IRB approvals, and informed consent forms would expedite the site start-up timeline. Investigator contract negotiation is also a time-consuming process with scope for added efficiencies. In Europe and other regions, these

forms are approved by the regulatory authority as part of the clinical trial protocol review, with only minor changes being made at the site level.

Recommended approach: Congress should encourage the adoption of a harmonized set of standards that would result in a process that is less expensive and more iterative, making use of electronic systems and decreasing the paperwork involved. There are existing models and options that could be built upon to expedite this process, including collaborative private-sector efforts in the U.S. and approaches in other countries. The Clinical Data Interchange Standards Consortium (CDISC), an organization Quintiles helped found and which I previously chaired, has established widely-regarded standards to support the acquisition, exchange, submission and archive of clinical research data and metadata.

Establishing Alternative Development Pathways

The Challenge

It currently takes an average of over seven years of total development time for New Molecular Entities,[3] including large, expensive Phase III studies required to demonstrate safety and efficacy in a broad population. This does not include the consideration that the risk/benefit relationship can differ sharply depending on the severity of the patient's illness and the availability of alternative therapies. Therapies that could benefit smaller subsets of populations take longer to develop in today's model and face the prospect of not reaching those specific patients because of the 'up or down' determination of safety and efficacy for the broader population.

The creation of the Breakthrough Therapy designation and expedited drug *approval* pathways is a welcome advancement, and we applaud the effort, including use of surrogate endpoints, early consultation for more efficient trial design, the increasing use of biomarkers, etc. However, the actual

[3] http://csdd.tufts.edu/files/uploads/Outlook-2013.pdf

time savings offered focuses largely on FDA review time (reducing from average of 10 months to six) versus providing a condensed *development* timeline, which currently ranges from 5-10 years to advance through the three-phase model.

A Solution

Quintiles strongly supports the adoption of alternative development pathways to speed the introduction of new therapies that would address unmet medical needs for patients with serious or life-threatening conditions. An example of this is the Adaptive Licensing approach that the European Medicines Agency (EMA) is now piloting.[4] In 2013, a similar alternative pathway approach was the subject of an FDA public hearing.[5] Under the FDA proposal, "the drug's safety and effectiveness would be studied in a smaller subpopulation of patients with more serious manifestations of a condition. Such a pathway could involve smaller, and more focused clinical trials than would occur if the drug were studied in a broader group of patients with a wide range of clinical manifestations. The use of biologically and clinically meaningful surrogates as non-mortality endpoints should be allowed. The labeling of drugs approved using this pathway would make clear that the drug is narrowly indicated for use in limited, well-defined subpopulations in which the drug's benefits have been shown to outweigh its risks." Allowance of such designs and endpoints should obligate Sponsors to conduct evaluations of longer-term, post-approval safety and outcomes.

Quintiles' research suggests that patients are willing to use therapies developed under an accelerated pathway. This is based in part on a 2012 survey of patients living with chronic disease, which found that patients want access to new medicines sooner, and that those in greatest need are willing to accept

[4] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce

[5] https://www.federalregister.gov/articles/2013/01/15/2013-00607/creating-an-alternative-approval-pathway-for-certain-drugs-intended-to-address-unmet-medical-need

more uncertainty about a new therapy if it offers potential to improve their health:[6] 71% of U.S. patients surveyed agreed that: "*We take too long to make drugs available, which costs lives by forcing people to go without potential beneficial therapies*.

Quintiles maintains not only that such a pathway is an important way to bring new therapies to patients in need, but also that it is a feasible pathway that can be operationalized today.

Recommended Approach

FDA should adopt, on a pilot basis for conditions meeting agreed criteria, an alternative development pathway where new entities meeting safety and efficacy endpoints (including clinically and biologically meaningful, non-mortality surrogates) in smaller, well-defined populations are granted limited market approval for that specific sub-population. The sponsor would then conduct additional studies on expanded populations to evaluate safety and potential expansion of label to broader population, while monitoring real-world outcomes in treated patients.

Today's technologies and science provide the ability to keep patients safe while accelerating access in ways not envisioned with the original Gold Standard three-phase randomized clinical trial (RCT) model. Below are five key capabilities to operationalize this approach. Each would improve drug development today. Together they would allow for the more aggressive step of allowing an Alternative Development Pathway. They would create a rigorous, confidence-inspiring pathway based on pre-registration studies in narrowly defined subpopulations, together with post-marketing registries and observational studies to ensure safe use:

[6] Quintiles. The New Health 2012 Report: Rethinking the Risk Equation in Biopharmaceutical Medicine. Available at: http://newhealthreport.quintiles.com/wp-content/themes/new_health_report/media/pdf/Quintiles_NewHealthReport_2012.pdf

a) **Data Analytics to Power Accurate Studies***:* The first key to making this work is being able to incorporate real-world data to inform trials. Quintiles and others have this capability and use it today. Congress should: 1) direct FDA to encourage its use; and 2) drive availability of de-identified data. This would enable better planning and design of pre-registration trials in stratified subpopulations so that these studies have the maximum likelihood of providing clinically and statistically significant findings. Advanced trial design tools are available now to incorporate real-world data into trial designs. For example, we use a tool called Quintiles Infosario™ Design that allows us to query real-world data including de-identified electronic medical records (EMRs) representing more than eight million patient lives. With this capability, questions such as "What are the anticipated event rates for specific sub-populations?" and "What sites are likely to see the specific populations eligible for this treatment?" can be answered. Those insights then can be used to perform simulations of possible trial designs in real time to yield more informative and efficient studies.

b) **Precise identification of the patient subpopulation**. Recent advances allow for the use of genomics, RNA sequencing, expression analysis, soluble and tissue-based biomarkers, and statistical methodologies to identify appropriate subpopulations. With these technologies, the patients who are most likely to benefit can be identified, optimizing the benefit-risk profile. However, we need FDA's continued acceptance and support of stratifying biomarkers as valid inclusion criteria and Congressional support of collaborative efforts to combine and study existing genomic data, and to encourage ongoing banking of samples.

c) **Higher-quality study sites to limit variability**. Smaller studies in stratified subpopulations intensify the need for research precision exceeding currently accepted levels. In order to limit variability, the accelerated pathway will require higher-quality study sites than are currently required for traditional studies. This could undermine the validity of smaller stratified trials. Collaborations with investigators and the use of sites that exceed existing quality and operational metrics will be necessary. Specialized sites are increasingly being used in clinical research. Others commenting to the Committee have called for the creation of Clinical Trial Networks that meet agreed upon standards. Quintiles supports this concept, yet suggests that Congress consider existing networks and standards established through current private sector initiatives. For example, Quintiles has a Prime and Partner Sites program that identifies and partners with sites and investigators who are capable of delivering these enhanced research capabilities, and monitors their performance with metrics and ongoing review.

d) **Real-world drug use in approved subpopulations**. Registries can be used to evaluate the efficacy and safety of a new therapy in the narrowly defined subpopulation in routine clinical practice for which safety and efficacy have been demonstrated in pre-registration studies. Observational studies can be used to assess real-world efficacy of the drug in all patient populations, even those not specifically evaluated in pre-registration studies. In our experience, the combination of well-constructed registries and scientifically rigorous observational studies augments insights gained from prospective pre-registration studies. It also provides knowledge about the benefit-risk profile of a drug in the real-world setting most relevant to practicing healthcare providers and patients.

e) **Monitor use of medicines in patients not participating in registries** to identify and evaluate off-label use. Prospective observational studies based on EMRs could be conducted to monitor medicine use in patients who are not enrolled in registries or observational studies. This would provide insight into the real-world use of the therapy and help to assess the percentage of prescriptions that are consistent with the labeled indication, the ways in which patients who utilize a drug off-label differ from the population for which the drug was approved, and the outcomes in such patients.

All the necessary pieces are in place to embrace alternative pathways for drug evaluation and approval. The tools and data required to identify and monitor patients correctly exist now. An integrated approach to the continuum of development and prescribing can be identified. To borrow from the technology world, we must "think big, start small, and scale fast" to make this alternative pathway a reality so that patients in need can benefit without delay. Congress should clarify, and if necessary amend, FDA statutes to allow and encourage the agency to adopt new pathways for development of new medicines, biologics and devices (rather than defaulting to an up or down vote on 'safe and effective').

Harmonizing Regulatory Requirements Internationally: Today's drug development is a global endeavor. What determines where drugs are tested and made available is often complicated and made more expensive by varying requirements for studies across geographies, including between the U.S. and EU. For instance, preparing different regulatory authorization applications for each country, for the same studies, requires enormous staff time and thus cost, with little benefit or meaningful differences. At times, different requirements for studies can even lead to the discontinuation or significant delays in advancing of promising development programs due to the prohibitive cost of doing large-scale studies differently for different authorities.

Quintiles has particular experience of the need for harmonization, having seen introduction of a promising program for a rare disease slowed by several years because one region required a trial with a placebo arm, the other (where a competitor product was marketed) required a trial including standard of care. Given the limited population for this investigational therapy, there were not enough patients to carry out both a placebo controlled and a non-placebo controlled study in a timely manner. This resulted in significant delay in making the drug available to patients and unnecessary cost of running separate studies.

Increased harmonization would reduce redundancies that have significant time and cost implications, and improve availability of medicines for patients who need them.

Recommended Approach: There has been a gradual move towards more harmonization through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH); this could be expanded and accelerated. The U.S. should increase cooperation and harmonization with other countries, starting with the EU, and consider mutual recognition of new drug regulatory authorization applications in the U.S. and EU. Congress should consider adding a goal to PDUFA 6, setting milestones for increased harmonization.

On behalf of Quintiles, thank you again for the opportunity to be part of today's discussion on modernizing clinical trials. I will be more than happy to expand upon any of the recommendations we have offered today, and look forward to your questions and participating further in the 21st Century Cures Conversation.