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JOHNSON & JOHNSON

BEFORE THE HOUSE COMMITTEE

ON

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CLINICAL TRIAL MODERNIZATION

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Testimony of Jay P. Siegel, M.D.

Speaking on behalf of Johnson & Johnson

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Good morning, Mr. Chairman and Members of the Committee. My name is Dr. Jay Siegel, and I am pleased to come before you today to offer a perspective on clinical trial modernization. As a physician, scientist, clinical trialist, research and development leader, and former public health officer, I am deeply troubled by two paradoxes. First, despite rapidly expanding biological knowledge and technology and increasing private spending on drug development, fewer new drugs reach patients each year than decades ago. Second, despite massive amounts of valuable medical data being generated and recorded every day, only a tiny fraction is being used to advance the health and welfare of patients by enhancing medical knowledge. I applaud this committee for its efforts in the 21st Century Cures Initiative and specifically for this hearing on clinical trial modernization as I believe that we now face an extraordinary opportunity to reinvent our approach to clinical trials and, as a result, to greatly increase the quality of medical care and the quality of life itself.

By way of introduction, I studied biology at the California Institute of Technology and received my medical degree from Stanford University with post-doctoral training at Stanford and the University of California, San Francisco. I worked 20 years regulating biologics at the Food and Drug Administration (FDA), including as the founding Director of the Division of Clinical Trial Design and Analysis. While at FDA, I had the privilege of working with leading clinical researchers in all areas of medicine, helping design and assess studies, and of helping create dozens of national and international guidance documents relevant to clinical trials.

For the past 11 years, I have served in various R&D leadership roles at Johnson and Johnson, where I am currently Chief Biotechnology Officer, and Head of Scientific Strategy and Policy. I have remained deeply engaged in clinical research issues and oversight, both internally and through participation in various organizations, including

the Biotechnology Industry Organization, the Society for Clinical Trials, and the Clinical Trials Transformation Initiative.

Clinical trials can be an essential tool in addressing the aforementioned paradoxes by turning scientific advances into medical advances and by ensuring that, as medical care is delivered, we learn from the collective experience. The way we currently think about, design, conduct, analyze, and regulate clinical trials has roots in an earlier era, when we lacked some powerful tools now available. We now have the opportunity to greatly enhance the power, efficiency and effectiveness of clinical trials. I will focus on four factors that enable such advances:

1. Use of electronic health records (eHR)
2. Use of biomarkers (e.g., genomics and proteomics), imaging, and informatics
3. Clinical trial networks, consortia, and disease-specific registries
4. Engaging patients as collaborators in the research process

1. ELECTRONIC HEALTH RECORDS AND RESEARCH IN THE CLINICAL CARE SETTING

The broad adoption of eHR enhances the potential to study health care efficiently in the settings in which it is being delivered. With use of eHR clinical research can be embedded into clinical care, creating what has been termed the learning medical system.

Electronic health records, if appropriately standardized and quality controlled, could provide highly valuable information to improve medical care. Efficient data collection through eHR could be augmented, where needed, with study-specific data collection forms integrated into the health record computer in the physician's office.

Using eHR, large scale registries of patients with a shared chronic condition could be constructed and data could be used for various purposes including studying risk factors and progression of the condition, to assess safety and other outcomes of treatment

alternatives in use, to validate biomarkers, and to identify potential participants for specific trials. The collection of data by eHR could be supplemented, when needed, with the power of random assignment to treatment alternatives to enable large simple randomized clinical trials conducted in care delivery settings, increasing the likelihood their results and learnings can be generalized to medical practice.

Perhaps the most valuable use of eHR-based studies in the clinical care setting will be to study interventions that are already in use (FDA approved, as needed), but where the best choice among available interventions is uncertain. However, eHR-based trials, particularly when employing supplemental data collection and randomization also have substantial potential to facilitate development of new medicinal products.

The availability of large registries would facilitate expansion of one of the more promising new approaches to clinical research – ongoing, adaptive clinical trials into which new, experimental therapies can be inserted for study. Based both on biomarker data and accumulating results, such adaptive trials can preferentially allocate subjects to promising treatments and discard non-beneficial treatments at an early timepoint. The recently launched Lung-MAP trial to evaluate therapies for squamous cell lung cancer is an example of such a trial. Similar approaches, facilitated by eHR (as well as by biomarkers and consortia), could greatly enhance the medical progress and development of treatments and cures across a broad range of diseases.

The power of eHR-based studies to enhance the ability to learn about the effects of medicinal products *after* market authorization (i.e., FDA approval) can have a profoundly positive effect on the frequency, speed, and efficiency of bringing new products, and new cures, to the marketplace. Information about a medical product's effects increases throughout its clinical usage, pre- and post-market. A key to effective regulation is the determination of where along that timeline sufficient information exists to warrant marketing authorization. The risks of approving products too early include the possibility that information important to the safe and effective use will be learned too late or not at all. But these risks must be balanced against the downsides of delaying access of patients

to important new medications by requiring additional information before approval. Also, the increased premarket costs and timelines that result from delaying approval to obtain more information can decrease the incentives for private investment in developing 21st Century Cures.

Given current limitations on the ability to gather information after marketing, data requirements (safety and otherwise) premarketing have been understandably and appropriately extensive. As eHR and learning health care systems enhance our ability to capture accurate information about a product's effect while on market, the risk of earlier approvals will diminish. Provided the regulatory process responds to this decreased risk, the result will be earlier availability of important therapies and increased investment in new treatments.

Realization of the potential for eHR-enhanced research in the clinical practice setting to augment the goals of the 21st Century Cures Initiative can be accelerated and optimized by addressing some key needs, including:

- *Standardization and interoperability of the eHR systems* so patients can be tracked and data compiled across multiple systems (e.g., different primary care systems, hospital records, cancer registries). Such standardization has been implemented in some countries (Scotland, Nordic countries) but is not in practice in the US.
- *Enhanced quality of data capture in eHR*. Training, standards, and incentives for physicians to capture complete and accurate data could enhance both medical care and medical research.
- *Research into how best to compile eHR data and use it both in clinical trials and in observational studies*. The Observational Medical Outcomes Partnership (OMOP), a public-private partnership including industry, FDA, and academics, has done much work in this area. More work remains and this should be a research priority.
- *Educating and incentivizing clinicians to become part of the learning system*, embedding studies into their process of clinical care.

- *Reassessing legal and regulatory frameworks to protect patients.* Current systems were designed in an earlier era and are likely not optimized to protect patients, or to ensure that they also support advances of clinical research utilizing eHR.

2. BIOMARKERS, IMAGING, AND INFORMATICS

Tremendous advances in our ability to collect and analyze many types of information about a patient and a disease state have greatly outpaced our ability to utilize such information. In particular, advances in genomics, proteomics and imaging hold the prospect to improve many aspects of how clinical trials are used in the development of new treatments.

I will briefly discuss four areas that could benefit from increased utilization in clinical trials of biomarkers and imaging:

- Accelerated approvals
- Personalized medicine
- Disease prevention and interception
- Adaptive design trials

Accelerated approval (biomarkers as surrogate endpoints)

The most reliable measures of efficacy of a treatment are direct measures of substantial patient benefit such as prolonged survival. But trials to assess such outcomes may need to be large and lengthy and their findings may be confounded by other therapies a patient may receive over the course of his or her disease. Use of biomarkers and imaging results that predict clinical benefit as surrogate measures of efficacy may allow more efficient clinical trials to support product approval.

Recognizing the potential utility of such surrogates, FDA, with congressional support, has for over two decades permitted use not only of surrogate endpoints validated to predict benefit, but also of those found to be reasonably likely to predict clinical benefit in serious diseases. Effects on the latter type of endpoint can support accelerated approval with a post-approval commitment to confirm benefit.

The acceptability of a surrogate as being reasonably likely to predict benefit is a matter of regulatory judgment. A key component of that judgment is assessment of the risk of being incorrect; that is, of approving a product based upon a surrogate endpoint when clinical benefit did not ensue. With the advent of new biomarkers and imaging modalities as potential surrogate endpoints, two arguments indicate that there would be net benefit to greater use of accelerated approval based on clinical trials with biomarker or imaging endpoints as surrogate endpoints. First, the vast majority of drugs approved to date under accelerated approval have had their benefit confirmed post-marketing. The benefits of accelerating, often by years, the availability of many important new therapies for serious diseases greatly outweighs the harms in those few cases where benefits have not been confirmed and accelerated approval was withdrawn. The fact that where it has been used, accelerated approval has brought tremendously positive results suggests that society would benefit from broader usage of accelerated approval, even where the risk of being wrong may be somewhat greater. Second, as noted above, the advent of eHR gives us a powerful new tool to assess drug effects in the post-marketing period. This reduces the risk that accelerated approval will lead to a situation in which actual benefits cannot be assessed or cannot be assessed in a timely manner.

Recognizing the desirability of broader use of accelerated approval, Congress, in the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, included language expanding the types of evidence FDA can use to assess whether a surrogate endpoint is likely to predict clinical benefit and encouraged usage of a broader variety of endpoints for accelerated approval, asking FDA to

> *"... implement more broadly, effective processes for the expedited development and review of innovative new medicines intended to address unmet medical needs*

for serious or life-threatening diseases or conditions, including those for rare diseases or conditions, using a broad range of surrogate or clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate."

It is too early to assess the impact of FDASIA on accelerated approvals. Given the potential benefits of broader usage of accelerated approval, it would be of value to follow up on efforts to realize the intent of FDASIA.

Personalized medicine (use of biomarkers to identify the best treatment for each patient)

Advances in next generation sequencing, imaging, and molecular diagnostics (e.g., proteomics), are contributing to our understanding of how and why drugs may have different effects in different individuals with the same diagnosis. Use of such biomarkers and imaging for entry and subset analysis in clinical trials will increase our ability to target treatments to those patients who will benefit most and/or be least likely harmed.

Disease prevention and interception (use of biomarkers to identify individuals at risk)

Advances in understanding the genetic and molecular basis of many diseases present an opportunity for advances in disease prevention and interception (i.e., the diagnosis and treatment of diseases at early stages to prevent progression and serious manifestations). The health benefits of disease prevention and interception over treatment are obvious. Prevention and interception also often offer substantial cost avoidance compared with treatment, although the savings may be delayed.

Despite these substantial opportunities, there have been relatively few clinical trials studying the prevention and interception of chronic diseases and cancer. One reason is that such trials can be rather large and lengthy, as it may be necessary to follow many research participants for a long time in order to see disease develop or progress in sufficiently large numbers to draw conclusions about an intervention. Biomarkers and imaging may help address these operational challenges of prevention trials. Such tests

can be used to identify patients at high risk for developing disease or progressing and may also be useful to detect progression.

Adaptive design trials (se of biomarker data to modify a trial)

The conventional approach to clinical trials is to lock in the design from the beginning. This approach lowers the risk of several types of bias. However, it potentially sacrifices efficiency by failing to make use of learnings during a trial to optimize design of the remainder of the trial.

In recent years, methodological advances have allowed greater modification of trials while in progress with limited risk of bias. Such trial designs are called adaptive designs. Advances in biomarkers and imaging enable adaptive designs by providing real time assessments of response to the intervention that can be used to modify the trial without having to wait for ultimate outcomes such as death.

Adaptive trials offer the opportunity to increase the efficiency of trials in translating science into medical knowledge, to accelerate drug development, and to ensure that more of the participants receive the more promising therapy. More experience with such trials should be encouraged as it will undoubtedly teach lessons on how best to deploy them. The Lung-MAP trial, referenced above, is one innovative example of a biomarker-driven, adaptive trial.

Implementation of biomarker usage other than for accelerated approval

Given that personalized medicine, disease prevention and interception, and adaptive trial designs have high potential value, the development and study of biomarkers and imaging to support these ends should be encouraged. Where such usages are shown to be associated with improved clinical outcomes, the regulatory process should be (and generally is) sufficiently flexible to allow that information to be incorporated into medical knowledge and practice.

3. CLINICAL TRIAL NETWORKS, CONSORTIA, AND DISEASE-SPECIFIC REGISTRIES

Government, in partnership with academia, patient groups, and industry can create and operate clinical trial networks that provide a rapid and efficient means for assessing new therapies either through ongoing large adaptive trials or through a series of trials. Well-run clinical trial networks can reduce the operational barriers, costs, and times of starting and conducting trials. The federal government can and should play an important role in creating and governing such networks, and involvement of a broader public-private partnership can help ensure that needs are met by bringing together experts and interested parties from diverse perspectives.

In some disease settings it may be appropriate for such a consortium to conduct a single ongoing adaptive trial to study many therapies (such as Lung MAP); in other settings it may be more practical to conduct a series of trials. Such consortia could and should also play a key role in creation and use of eHR-based registries and trials as discussed above.

Clinical trial networks have been operational and have achieved success in several disease areas. Currently, the creation of a broad collaboration or consortium to develop a registry, to identify cohorts, and to design and conduct trials is being implemented through IMI-EPOC-AD: the Innovative Medicines Initiative European platform for Proof of Concept for prevention in Alzheimer's disease.

4. ENGAGEMENT OF PATIENTS AS COLLABORATORS IN THE RESEARCH PROCESS

The traditional paradigm for clinical research places patients in the position of subjects – a relatively passive role. But patients bring to the clinical research far more than a disease or condition; they bring valuable perspectives and insights. Furthermore, many

patients are strongly motivated to participate in research, both to benefit their own care and altruistically, to benefit future patients with a similar condition. Enhanced patient engagement can benefit the clinical trial process in various ways, including the following:

- *Patient-reported outcomes:* Often investigators and regulators have defaulted to use of outcome measures that can be objectively measured. However, the outcomes most important to patients, those reflecting how they feel, are generally best obtained directly from patients.
- *Patient-informed risk-benefit assessments:* Usage of virtually all therapies is associated with some risk of adverse effects. So in the regulatory decision process, safety is not an absolute; rather the acceptability of the safety profile of an intervention must be determined in the context of potential benefits. Patients can provide a unique and extremely valuable perspective on the impact and relative value of various demonstrated benefits and risks.
- *Improved trial design*: Patient involvement in trial design can enhance recruitment, adherence, relevance, and tolerability of trials.
- *Enhanced enrolment of patients in clinical research*: A critical prerequisite to developing an effective learning medical system with medical research embedded into care settings is to expand and diversify enrolment into clinical trials. We must move from a situation in which study volunteers are a select, rather non-representative group of patients to one in which they are a much larger, diverse, broadly representative group who represent well those to whom results will be generalized. That end can best be accomplished if all involved parties, including government agencies such as NIH, NSF, and FDA work to engage the public, educating people about the value of participation in clinical research while dispelling common misperceptions. Broader voluntary participation in trials will improve both their speed and their generalizability, bringing treatments to patients sooner, and with more information.

CONCLUDING REMARKS

Again, I wish to thank the Committee for its attention to this important matter. As I have described, several opportunities are before us, through advances in clinical trials, to improve the translation of scientific advances into medical advances and patient cures, and to ensure that more of the vast amount of medical data created and recorded every day are used to improve the care of patients and advance medical knowledge. The result will be nothing less than longer and healthier lives.

Executive Summary of Testimony of Jay P. Siegel, M.D.
Speaking on Behalf of Johnson & Johnson
House Committee on Energy and Commerce, July 9, 2014

Clinical trials are the tools by which our society translates scientific advances and product discoveries into advances in medical care. Johnson & Johnson welcomes the opportunity to participate in efforts intended to improve the effectiveness and efficiency of clinical trials. There are various opportunities for such improvements that will greatly facilitate advances in health care. We emphasize four areas of opportunity.

First, the adoption of electronic health records (eHR) can enable great advances in research in the clinical care setting. Properly deployed, eHR can enable extensive and rapid data collection with limited disruption to the clinical care process. Large patient registries can be created to study a specific disease and its treatments and to enable randomized trials employing eHR in data collection. Improvement in ability to obtain data from use of products post-approval should, in some cases, enable earlier approval and availability of valuable new therapies. Realizing this potential will require addressing several issues, including: standardization and data quality of eHR systems, enhanced provider and patient education and participation, research into how best to compile and use eHR data, and reassessment of regulatory frameworks.

Second, scientific advances in identifying biomarkers and imaging modalities, when applied in clinical trials, can greatly enhance our learning and progress. Increased usage of biomarkers for accelerated approval can be expected to accelerate availability of important new therapies more broadly, as it has for HIV infection and cancer. Increased usage of biomarkers in clinical trials can also be expected to advance: 1) personalized medicine, by identifying patient characteristics that help determine the best therapy, 2) the study of disease prevention or early treatment (interception) by identifying patients at substantial risk of developing disease or experiencing progression, and 3) the utility of adaptive trial designs, in which information learned during a trial is used to improve the trial design and ability to address key questions.

Third, creation of clinical trial networks involving consortia of government, academia, patient groups and industry can provide a rapid and efficient means for assessing new therapies, in either ongoing large adaptive trials or through a series of trials. Such consortia could also assemble and utilize eHR-based registries.

Fourth, increased engagement of patients as collaborators in the research process can bring about improvements in how we measure the effects of an intervention (patient reported outcomes), in how we assess risks vs. benefits, and in clinical trial recruitment, adherence, relevance, and acceptability. Broad education about the benefits of clinical trial participation could help bring about greater participation, facilitating creation of a learning health care system and accelerating advances in medical care.