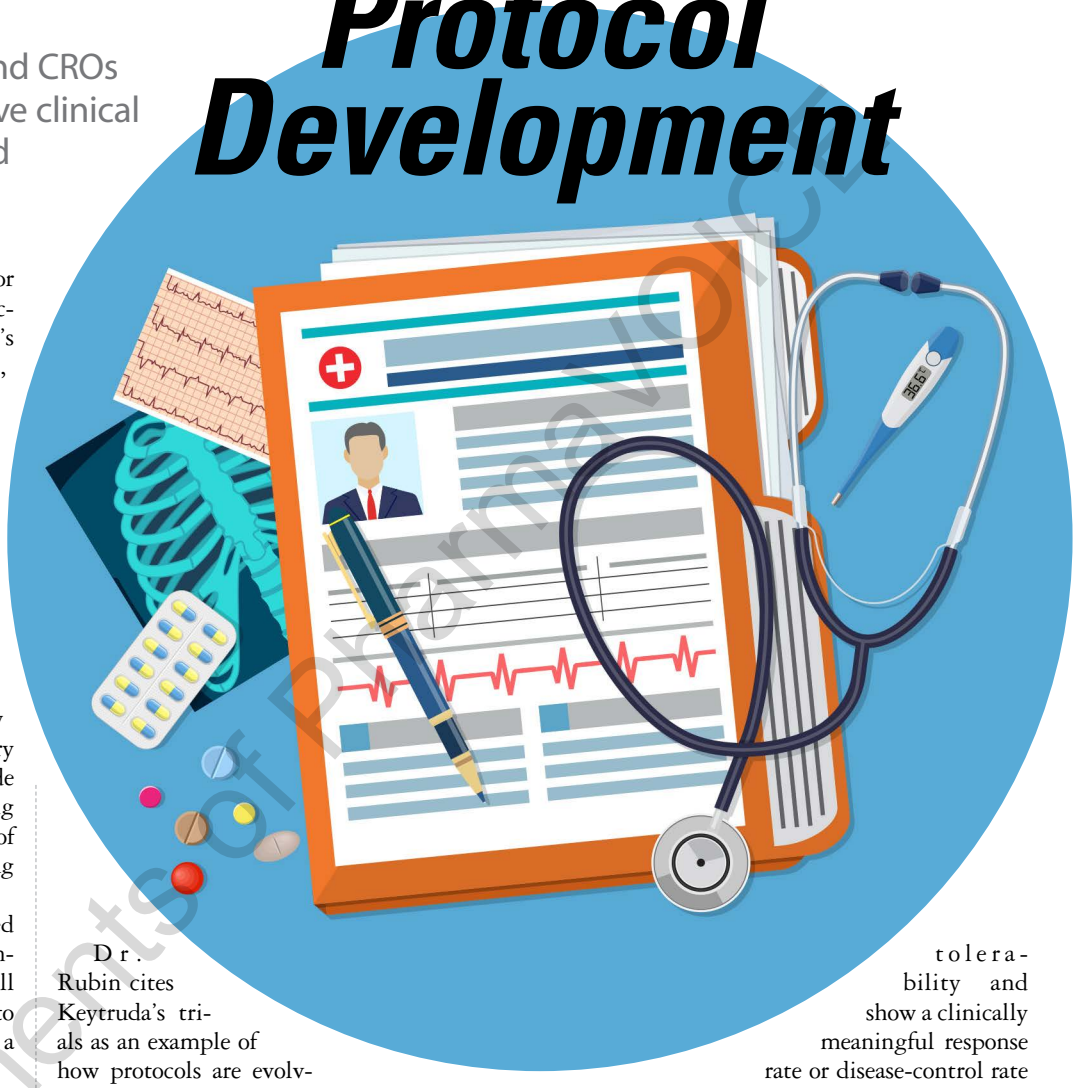
By Denise Myshko

TRENDS IN Protocol Development

Pharma company sponsors and CROs are looking to adopt innovative clinical trial designs as a way to speed development.



Clinical protocols are the framework for a clinical trial. They provide the structure for assessing a potential product's safety and efficacy. But over the past 15 years, protocols have increased in endpoints, procedures, eligibility criteria, number of CRFs, protocol amendments, and investigative sites, according to the Tufts Center for the Study of Drug Development.

Protocols have become much more sophisticated over the last 20 years, says Gerry Messerschmidt, M.D., chief medical officer at Precision Oncology.

"When I was writing protocols 20 years ago, they were one-third the size that they are now," he says. "The change has really been quite dramatic. Now, protocols are very clear on all of the elements needed to include human subjects in a clinical study, ranging from all of the steps to protect the safety of patients to the actual investigational drug specifications."

Dr. Messerschmidt adds that the added complexity extends from negotiating a contract with a site, to allowing patients to enroll in clinical studies, to government issues, to scientific medical issues, which is having a particularly major impact.

"For example, since the completion of the Human Genome Project, the underlying causes of cancer have begun to be explored much more deeply," he explains. "Our understanding today of cancer, and frankly of other diseases as well, is much more in-depth than it was even five years ago. I anticipate this type of in-depth learning and understanding of the basic mechanisms of the diseases that we're treating will become more complicated in the next five years."

There is an effort in the industry to increase the speed in which effective drugs reach patients, says Eric Rubin, M.D., VP, therapeutic area head, oncology, early development, Merck, noting that the traditional path of clinical trials for oncology has changed quite a bit over the last five years.

"We've gone from the classic idea of a Phase I, Phase II, Phase III trial to a seamless trial," he says.

Dr. Rubin cites Keytruda's trials as an example of how protocols are evolving. Keytruda (pembrolizumab) is a humanized monoclonal antibody approved to treat advanced non-small cell lung cancer, advanced melanoma, and head and neck squamous cell cancer. The product works by increasing the ability of the body's immune system to help detect and fight tumor cells. It blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes.

The development of Keytruda used an adaptive trial approach, Dr. Rubin says. An adaptive trial includes preplanned adaptations of one or more specified clinical trial design elements that are modified and adjusted while the trial is underway based on an analysis of interim data.

KEYNOTE-001, the trial used to support Keytruda's first approval in melanoma (2014), was opened in 2011. That study was done in six parts to assess pembrolizumab's safety and tolerability and show a clinically meaningful response rate or disease-control rate in patients with melanoma and non-small cell lung cancer.

"An adaptive trial can significantly speed up obtaining information that's needed for the FDA to enable an approval and make drugs available to patients much faster than would have been the case, if the traditional clinical trial paths were followed," Dr. Rubin says.

When used appropriately, adaptive trials can provide good information, says Fez Hussain, M.D., medical VP and global head immunology and internal medicine, and head of GI centre of excellence, QuintilesIMS.

"The general idea is to try to compress the timelines or provide more information than would be possible with a conventional study design," he says.

Adaptive trials are being used in about 20% of Phase II and Phase III trials, reports Sy Pretorius, M.D., senior VP and chief scientific officer, Parexel.

"Adaptive trials and platform designs are becoming more popular to help reduce time and cost," he says. "These approaches also help to make sure we have patient-centric protocol designs. Companies, such as Parexel, use focus groups, disease foundations, patient interviews, and social media among other things to ensure that the patient is and remains central to the design."

Across the industry, simple adaptive designs are being used with about 20% of clinical trials, according to the Tufts Center for the Study of Drug Development. Companies that participated in a senior leadership roundtable reported that they expect the adoption of adaptive trial designs in exploratory phase clinical trials to increase significantly over the next several years.

Adaptive clinical trials allow modification of trial design based on observation, including alterations to dosage, sample size, therapy, and patient selection criteria. The FDA endorsed adaptive designs in clinical trials as part of its Strategic Path Initiative in 2004. The agency then released a draft guidance document for adaptive designs in studies of drugs or biologics in 2010, and in May 2015 regulators issued a similar document for devices.

According to Tufts, the most common adaptive strategy is "futility stopping," where trials are cancelled if the treatment fails to reach a pre-determined level of effectiveness. Sponsors, Tufts finds, have been slower to adopt more complicated designs, with fewer than 10% of clinical studies trying strategies such as "seamless" transitions from one stage of research to another or dynamically designed dose-finding.

At the same time, a cross-functional protocol development process that incorporates a combination of real-world evidence and real-world design is becoming more popular, says Ian Shafer, managing director in Accenture's global accelerated R&D services group.

"This is where the science meets feasibility," he says. "There are great examples of well-written protocols that have failed to enroll a single trial or a single patient because they didn't take into account the feasibility of the trial."

Companies are beginning to push the envelope of what clinical designs look like and breaking down some of the traditional processes.

"We're starting to see the decomposition of the traditional clinical Phases I, II, and III studies, and there are more novel clinical trial designs, such as basket or umbrella trials, that are challenging the norm of clinical trials," Mr. Shafer says.

Nick Kenny, Ph.D., executive VP, oncology and hematology, INC Research, says

> We are seeing fewer very large studies targeted toward a general population of people with a certain condition and more small studies for very specific patient populations.
>
> **DR. LINDSAY MCNAIR**
> WIRB-Copernicus Group

seamless designs place a different set of requirements on the sponsor, the CRO, and the site.

"From the sponsor side, the protocol has to be finalized, and there has to be an agreement with the agency," he says. "Sponsors have to make the financial and operational commitment that when they build, for example, the databases that the design and data outputs will be submission ready. The CRO and the site have to ensure constant data currency. This puts a bit of added pressure on sites that are often busy. While those seamless designs are certainly on the rise and potentially can bring drugs to market faster, with shorter trials and fewer patients, they require an added commitment by the sponsor, CRO, and site to keep the process very tight right from the get go. There's not the same paced approach as there was in the past with the traditional Phase I approach."

Dr. Kenny says one of the factors driving the use of seamless trials is science.

"Looking at lung cancer science, for example, about 4% of the available patients have a specific mutation," he says. "It makes sense that if the drug being investigated targets that specific mutation, the clinical point can be made using a smaller number of patients because they're already highly selected for particular molecular aberrations. The data that can be generated from a positive on-target response compared with data from a traditional all-comers trial is much higher based on fewer

Protocol Amendments a Challenge

Protocols have at least one amendment, which comes with substantial cost, cycle time delays, and operational complexity. A Tufts Center for the Study of Drug Development study in 2016 found that the most common causes of protocol amendments are regulatory agency requests, new safety, or dose-related information about the study drug, new standards of care, competitive pressures, protocol design inconsistencies and flaws, and patient recruitment difficulties.

A high percentage of amendments occur before first patient first dose, and suggest the need for better up-front planning and review of the protocol before release, especially for avoidable changes such as design flaws and patient recruitment difficulties, say researchers at Accenture.

Fez Hussain, M.D., medical VP and global head immunology and internal medicine, and head of GI centre of excellence, at QuintilesIMS, says protocol amendments can have a negative impact on studies.

"Protocol amendments can change the patient population, and that may sometimes be a challenge to validity," he says. "Secondly, logistically, amendments have to go through regulatory authorities, and then be implemented at the site and country levels."

Half of protocol amendments are related to eligibility criteria, explains Sy Pretorius, M.D., senior VP and chief scientific officer, Parexel.

"Assessing feasibility in a diligent manner is critical," he says. "Data from electronic health records, insurance claims, social media, and many other sources are very helpful in assessing feasibility and doing so properly. Having the data is one thing but deriving appropriate feasibility insights that can be built into a protocol and into the design is critically important."

WIRB-Copernicus Group Chief Medical Officer Lindsay McNair, M.D., says sometimes protocol amendments, while challenging, can't be prevented because new information comes to light that wasn't available at the start of the study.

"One way to try to avoid amendments is to look critically at every part of a protocol, especially parts that are taken from a prior study with the same investigational product," she adds. "Sometimes, for example, an exclusion criterion that was necessary in the early studies gets carried over into later protocols, and limits eligibility unnecessarily until it is removed. One great movement toward reducing protocol amendments is the incorporation of input and feedback from

patients and caregivers early in protocol development, to avoid visit schedules and procedures that will burden participants so much that they won't enroll or will leave the study early, leading to amendments to try to improve enrollment or reduce drop outs."

Eric Rubin, M.D., VP, therapeutic area head, oncology, early development, Merck, says managing amendments — the initial trials for Keytruda had eight protocol amendments — requires rigor on the sites' part and it may also require changes to data collection, and that adds complexities.

One way to minimize the impact of changes, says Accenture, is to bucket multiple amendments into one change, which would reduce the cost of IRB fees and vendor contracts.

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>
> **IAN SHAFER**
> Accenture

patients. These studies can be powered appropriately with fewer patients."

Dr. Kenny adds that it is incumbent upon the industry to continue to drive innovation and encourage stakeholder collaboration and data sharing. Nevertheless, as noted clearly by FDA's Dr. Padzur, any seamless trial design (such as Phase I studies with multiple expansion cohorts) should be critically reviewed for strong scientific rationale, appropriate patient safety measures, and early consultation with regulatory authorities.

Dr. Hussain points out that one challenge related to adaptive designs is unblinded data.

"It's really important that the number of people involved in that interim analysis is very small and they're completely firewalled from other study issues," he says, adding other challenges relate to technology, which needs to enable rapid and accurate collection of that data.

Basket and Umbrella Trials

Basket and umbrella trials are the newest trends in protocol designs. Basket trials enable the study of multiple molecular subpopulations of different tumors or histologic types within one study based on a common genetic mutation. Umbrella trials are two or more sub-studies that are connected through a central operational infrastructure with a focus on a single tumor type.

These types of trials enable sponsors to target a particular patient population using biomarkers, and oncology is one of the areas in which these types of designs are being used.

Dr. Kenny explains that by screening patients for multiple aberrations within a specific tumor type — under an umbrella trial design — they can be appropriately allocated to the treatment arm that matches the targeted therapy for their molecular abnormality. Alternatively, he says a basket trial design allows patients to be screened independent of tumor type for a particular aberration and are treated with the targeted therapy for that abberration.

While scientific innovation, and accelerated trials, is imperative, the bar is not lowered when it comes to patient safety and proof of efficacy.

One example of a basket trial is the I-SPY trials for breast cancer. I-SPY 2 was launched in 2010 and is a clinical trial for women with newly diagnosed, locally advanced breast cancer to test whether adding investigational drugs to standard chemotherapy is better than standard chemotherapy alone before having surgery.

The trial is sponsored by the Biomarkers Consortium, a partnership led by the Foundation for the National Institutes of Health, the FDA, the National Institutes of Health, and a large number of partners from major pharmaceutical companies.

A feature of the trial is that it screens multiple drugs from multiple companies, up to 12 different cancer drugs, over the course of the trial. This allows the I-SPY 2 team to graduate, drop, and add drugs throughout the course of the trial without having to stop the trial to write a new protocol.

In July 2016, two products "graduated" from the trial into their own clinical programs. One product is neratinib from Puma Biotechnology. The company has since filed with U.S. and global regulatory authorities for neratinib for the extended adjuvant treatment of patients with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab (Herceptin)-based therapy. It is also in a Phase II basket trial as a single agent in patients with solid tumors who have an activating HER2 mutation.

The second product is veliparib from AbbVie in combination with carboplatin, which is being studied in a Phase III trial. It is also being studied in more than a dozen cancers, including Phase III studies in advanced squamous and non-squamous non-small cell lung cancer (NSCLC) and ovarian cancer.

Another example of the basket trial design is the NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) Trial, which is being run by the NIH for advanced solid tumors,

lymphoma, or myeloma. Each treatment is a unique arm of the trial. The trial began enrolling in August 2015; there are 24 treatment arms and each arm enrolls 35 patients.

Patient organizations are also supporting basket and umbrella trials. One such trial is Beat AML, sponsored by the Leukemia and Lymphoma Society (LLS) and launched in October 2016. This is a master clinical protocol for acute myeloid leukemia patients based on a personalized medicine approach. LLS is collaborating with academic researchers, pharmaceutical companies, a genomic provider, and a clinical research organization. Initially, there will be five trial sites.

The four participating biopharmaceutical companies — Alexion, Boehringer Ingelheim, Celgene, and Gilead Sciences — in the Beat AML Master Trial are offering the following investigational drugs, respectively: samalizumab (ALXN6000), BI 836858, enasidenib (AG-221/CC-90007), entospletinib.

"We now have the tools to thoroughly dissect a patient's tumor type, and we know that the tumors are all different, but they share certain genetic mutations," Dr. Rubin says. "We and others are developing drugs to target those particular mutations. It may become more logical then to develop a trial for a particular mutation rather than develop a trial for a particular tumor type."

Dr. Rubin says one challenge of these trials is oftentimes the rigor of the needed tests before the trial could slow the actual clinical study.

"For DNA sequencing, for example, there's a lot of discussion around what exactly needs to be shown for these tests to enable selection of patients for treatment," he says. "Next generation sequencing, or the deep DNA sequencing of a patient's tumor, is becoming standard of care, and at this point, there are many such tests that can be run either by a hospital or a cancer center."

Mr. Shafer says these trials require a much broader set of internal resources to execute, from recruiting of patients and investigators to CRAs to data management.

"There is a ripple effect when the complexity of the design is compounded, which leads to implications to the overall execution analysis and subsequent reporting of the clinical trial," he says. "The question becomes, can more value be derived by combining and integrating trials under a single basket design, versus running independent trials? My gut says yes."

Dr. Messerschmidt says about 15% to 20% of the trials Precision Oncology does are basket trials.

"These trials are not overwhelmingly taking over the clinical trial space, but they do have a role to play in trying to bring products to market a little bit more efficiently," he adds.

Managing Clinical Trial Complexity

In an effort to increase efficiency and reduce costs, more companies are employing quality by design principles, says Adrian Hernandez, M.D., director, Health Services Outcomes Research, Duke Clinical Research Institute, and DCRI Faculty associate director, professor of medicine, cardiology.

"The idea is that that less may be more," he says. "If a protocol calls for fewer procedures there is a need for less data capture. The trial is more focused and could result in better quality results because of better participation, better retention, and fewer errors because the protocols are less complicated."

Companies are always looking for ways to better select patients, better identify efficacy, and look at different outcomes, says Barbara White, M.D., chief medical officer at Corbus Pharmaceuticals.

"Patient selection, increased number of outcomes, and new outcomes all add to the complexity of trial design," Dr. White says. "The more restrictions on eligibility and the more measurements that are needed, the more opportunities there are for a site to make mistakes."

Dr. White says there needs to be a balance between inclusion and exclusion criteria.

"There's a definite balance between being inclusive enough to get a sense of what the safety profile and the efficacy might look like," she says. "But they can't be so inclusive that questions can't get answered."

There are external pressures on companies to make sure any safety risks are mitigated, therefore protocols are often intense with added procedures to ensure any scenarios are understood regardless of how likely they will be, Dr. Hernandez says.

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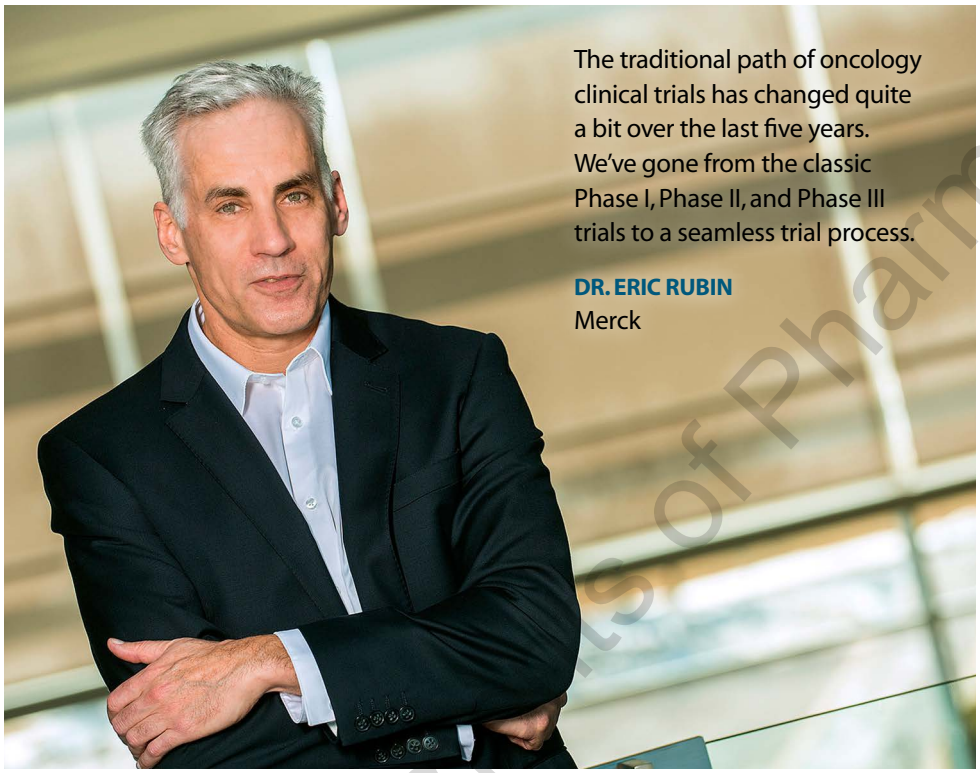

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DR. ERIC RUBIN
Merck

meeting the primary objectives and don't necessarily add any value," he adds.

Protocols have certainly become more complex, although it is hard to say when they become too complex, says WIRB-Copernicus Group Chief Medical Officer Dr. Lindsay McNair.

"There are a number of drivers," she says. "Certainly, scientific advances in genomic and biomarker research have influenced this trend, as has the movement toward precision medicine. We are seeing fewer very large studies on a general population of people with a certain condition and more small studies on a very specific population. This is leading to more and more detailed, protocol eligibility criteria. Protocols are including more exploratory endpoints and biomarker sample collection to obtain as much data as they can, which adds to the number of procedures."

The number of procedures, the number of visits, the number and disparate types of data that are being collected is exploding, Mr. Shafer agrees.

"When wearables and sensors are added to trials, the burden on the investigators, the burden on the operations, and the burden on the patient continue to increase," he says. "Companies may find themselves with a scientifically sound protocol that can't be executed upon."

Dr. Hussain says a number of factors are contributing to the increase in protocol complexity, including regulatory requirements, advances in technology, biomarker strategies, and global studies.

"With global studies, there are regional variations in the standard of care that may need to be incorporated," he explains.

Dr. McNair says from an operational perspective, looking for smaller numbers of study participants with very specific characteristics also has implications for clinical site selection.

"Studies need fewer sites, but the sites must have those specific patients," she says. "This has led to the increase in just-in-time site networks; rather than opening many sites and hoping that the participants will be there, sites are prepared to open a study very quickly when an eligible participant is identified."

Mr. Shafer says companies need a well-thoughtout program design to capitalize on some of these advances.

"I'm starting to see more intelligent designs and new technology to support patient population modeling and the ability to intelligently link objectives to procedures and to endpoints to solidify the integrity of the trial design." PV

Clinical Trial Design Categories

- **Adaptive Trials:** A study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of interim data from subjects in the study
- **Basket Trials:** Enables the study of multiple molecular subpopulations of different tumor or histologic types within one study based on a common genetic mutation.
- **Enrichment/Targeted:** A random control trial that incorporates biomarker to identify specific patients to assign appropriate therapies
- **N-of-1:** An individual patient is considered the sole unit of observation in a study investigating the efficacy or side-effect profiles of different interventions
- **Randomized Control:** Most common trial design where the only expected difference between the control and experimental groups is the outcome variable being studied
- **Umbrella Trials:** Two or more sub-studies that are connected through a central operational infrastructure with a focus on a single tumor type of histology

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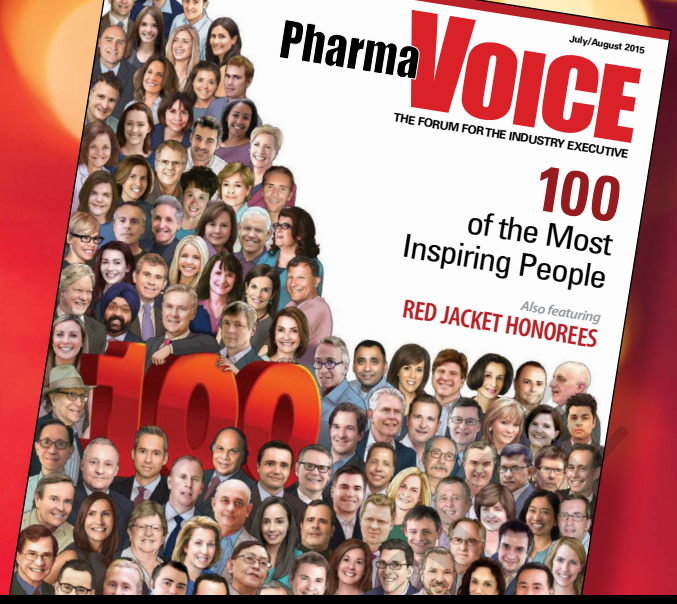

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