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DIA 2017 Digest

Key Coverage From This Year's Conference

Dear Pharma Executive,

From pricing to P-values, the Drug Information Association's annual meeting offered lively discussion on critical regulatory and policy issues. Our editorial team was among the throngs in Chicago this month, dissecting podium presentations from FDA officials and hearing the latest company gossip on the exhibit hall floor. The stories we've compiled in this report offer a distillation of many of the trends driving business decisions today, and our reporting illuminates the personalities of many of the key actors driving those events.

As travel often is, the trip was both exhilarating and exhausting. Whether you've attended DIA for years or are learning of the event for the first time in these pages, we hope these stories (supplemented with some of our recent related coverage) will give you an opportunity to reflect on the state of the industry – one that seems to have more development possibilities but all with more potential pitfalls than ever before. With real-world data, for example, companies see the promise of swift supplement approvals – but only if they can convince the rest of the health care system to collaborate with them. And as the pharma industry contemplates how best to partner with others, FDA must struggle with how to work with itself as combination products and other scientific advances challenge the fundamentals of its regulatory scheme and even its organization based around product centers.

We'd love to hear your impressions of DIA, and whatever you think of the state of industry, anytime. Drop me a line: Nielsen.Hobbs@informa.com

Happy Pharming,

Nielsen Hobbs

Executive Editor, US Regulatory & Policy
The Pink Sheet/Scrip

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RX PRICING:
Adversaries Search For Common Ground On Value-Based Contracts

By Brenda Sandburg

Photo by Brenda Sandburg

Sudip Parikh, Senior VP & Managing Director, DIA Americas; Joel Beetsch, VP, Patient Advocacy Group, Celgene; Shawn Davis, Senior Director, Formulary Solutions, Express Scripts; Phillip Lerner, VP & National Medical Director, Aetna; Sloane Salzberg, Executive Director, Prescriptions for a Healthier America

Adversaries in the debate over Rx drug pricing called a truce in discussing value-based payments. But they voiced the usual themes of the need for shared accountability and transparency in pricing decisions.

Speaking on a panel at the Drug Information Association's annual meeting in Chicago June 20, **Aetna Inc.** VP and National Medical Director Phillip Lerner said the disagreements between industry, pharmaceutical benefit managers and insurance companies are subtle. In deciding if there is sufficient evidence to make a decision about a drug there is "an interpretation as we are evaluating a clinical study or manufacturing data or the medical literature. It's a little bit of an art, a little bit of a science," he said.

Shawn Davis, senior director, formulary solutions at **Express Scripts Holding Co.**, agreed that evaluating data and figuring out which medication will work best for a patient can indeed be in some sense subjective. But he said there is an argument about what is driving the cost increases, and "how transparent manufacturers want to be is a question for debate."

Joel Beetsch, VP of **Celgene Corp.**'s patient advocacy group, said the disagreement among the panelists is over whether pharmaceutical costs are too high and the price is being calculated in accordance with outcome and value. And there is a question as to whether a payer is charging premiums that may be out of line with the services provided. He emphasized the need for shared accountability between all the stakeholders.

"It's like going to a casino," he said. Everyone willing to gamble is prepared to lose some money. "Shared accountability requires us all to come to the table with a little something to lose so the winner is the patient."

How To Lower Drug Costs

Panel moderator Sudip Parikh, senior VP and managing director, DIA Americas, asked the speakers what in a perfect world they would like to see happen in the next couple of years to solve the problem so his mom sees lower drug prices.

Beetsch rattled off three things on his wish list: shared accountability and transparency of the process;

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better collection and assembly of data; and more patient involvement.

Davis cited the need for data sharing, noting that two large hospital systems in St. Louis do not share data with each other. And Lerner said he wanted to see more of a shift in paying for value throughout the health care system.

"Drugs are one piece of the whole health care picture," Lerner said. We also need to look at other factors that determine whether someone is ill, including compliance, case management and follow-up. We need to "look at how drugs are used in the context of overall clinical care and pay for drugs based on their clinical outcomes or at least their contribution to clinical outcomes."

Audience Members Challenge Panelists

While the panelists were cordial, audience members were unusually heated in their responses. When Davis compared variation in drug pricing based on prescription volume to the different amounts people pay for cars an audience member interrupted him, shouting out that lives are not cars.

During the question and answer period, a representative from **Bristol-Myers Squibb Co.** who works in clinical development pointed out that administration represents 25%-30% of health care costs and asked the panelists how they are addressing efficiency in their administration. "You talked about competition and hoping it will drive down value. The evil twin of competition is fragmentation and everything we do to address fragmentation is administration costs," she said, drawing applause from the audience.

Another audience member said the panelists' discussion did not address the delivery system, particularly in the physician office, and decried the inability of experts in this area to have a voice in setting policy.

Photo by Brenda Sandburg

Shawn Davis, Senior Director, Formulary Solutions, Express Scripts

And another member of the audience angrily asked what the panelists were doing to make sure that everyone gets to see the health care bill being drafted in the Senate to repeal the Affordable Care Act. "You've all talked about transparency, education, knowledge. What have you done?" she asked.

Panelist Sloane Salzberg, executive director of Prescriptions for a Healthier America, responded that no one has seen the language in the bill and that members of her coalition have sent multiple letters and requested information about the legislation.

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AstraZeneca's 13 Outcomes-Based Contracts Show "Proactive" Engagement On New Models

By Jessica Merrill

AstraZeneca PLC has signed two new outcomes-based reimbursement contracts with Harvard Pilgrim Health Care for the blood thinner *Brilinta* (tocagrelor) and the diabetes drug *Bydureon* (exenatide extended release), bringing the total number of the company's value-based reimbursement contracts to 13.

The double-digit number represents a significant amount of contracts in what is an exploratory area for the industry, as pharma manufacturers and insurers attempt better align the cost of medicines to value.

> **"What's really important about outcomes-based agreements is they are dynamic ... We know we have to morph as we glean insights..."**

The latest two contracts, announced May 30, are part of an initiative at AstraZeneca to be a leader in innovative reimbursement models, VP-Market Access Rick Suarez said in an interview.

"We keep proactively engaging our major national [pharmacy benefit managers] and many regional PBMs to really challenge them on how we can demonstrate the value of the products AstraZeneca brings to the market," Suarez said. "I think it just reflects the value of our medicines and also our commitment at AstraZeneca to really be a leader and a differentiated pharma company as it pertains to this type of work."

The company's 13 contracts span three therapeutic areas, oncology, respiratory disease and cardiovascular/metabolic.

"Agreements like this with Harvard Pilgrim are the perfect example of making sure we are putting patients first," Suarez said. "Let's tackle the types of disease states that are the most costly and the most endemic in the US."

That's one of the reasons why Brilinta and Bydureon are two strong candidates to serve as the basis of an outcomes-based contract, he said. Another reason these drugs have been selected is technical, because taking them can lead to a clearly-defined measurable outcome to help tie reimbursement to value.

"Those medicines in my opinion are prime to demonstrate the impact AstraZeneca can have in cardiovascular disease and cardiovascular disease associated with diabetes," Suarez said.

Defining an appropriate outcome to measure, often within a relatively narrow timeline, can be one of the challenges when it comes to developing these types of contracts, despite significant interest among manufacturers and payers. *(Also see "Outcomes-Based Contracts Aren't So Easy, Harvard Pilgrim Cautions" - Scrip, 2 Jun, 2016.)*

Cardiovascular disease has emerged as one of the first categories to be targeted, with several deals in place for drugs like **Novartis AG**'s heart failure medication *Entresto* (sacubitril/valsartan) and **Amgen Inc.**'s PCSK9 blocker *Repatha* (evolocumab). AstraZeneca previously had an outcomes-based contract with **Cigna Corp.** for its cholesterol drug *Crestor* (rosuvastatin) that involved using pharmacy and medical claims to assess beneficiaries' risk for atherosclerotic cardiovascular disease and giving those beneficiaries at highest risk more unrestricted access to the drug.

Brilinta Tied To Hospitalizations, Bydureon To HbA1c

In the case of Brilinta, under the agreement with Harvard Pilgrim, the outcome that will be measured is reduction in hospitalizations for repeat acute coronary events versus patients on another oral antiplatelet therapy, clopidogrel. The Bydureon contract focuses on HbA1c as an outcome measure, and the ability of patients who adhere to Bydureon to get to a predetermined HbA1c goal.

If either medicine fails to meet the agreed-upon outcome criteria in patients, AstraZeneca will pay a steeper rebate.

AstraZeneca has several other outcomes-based reimbursement contracts in place for Brilinta, but the deal with

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Harvard Pilgrim represents the first such arrangement for Bydureon. The company is working on similar deals for Bydureon as well as for another diabetes drug, the SGLT-2 inhibitor *Farxiga* (dapagliflozin).

Harvard Pilgrim will collect the data and provide blinded patient-specific and median patient results to AstraZenca, as well as information on adherence.

"It's very important for us to understand that each and every patient were adherent to our medicines and where they got from an HbA1c perspective, and then we have different options we put into the market in how we contract with our payers in terms of their eligibility to have additional rebates if the product works," Suarez said. "Each arrangement is a little different."

Both of the Harvard Pilgrim contracts span three years, but there is an opportunity for AstraZeneca and the insurer to check in annually to evaluate progress.

With Experience, Lessons Learned

"What's really important about outcomes-based agreements is they are dynamic. They are not stagnant and that is something I've very proud of for AstraZeneca," Suarez said. "We know we have to morph as we glean insights from these innovative contracts and [the agreements] afford us the opportunity that possibly in the middle of the year we need to make some tweaks and changes."

This deal with Harvard Pilgrim is linked entirely to rebates and does not include any kind of formulary advantage or priority access, as is sometimes the case with outcomes-based reimbursement contracts. For example, under Amgen's outcomes-based contract with Harvard Pilgrim for Repatha, the insurer agreed to limit some access restrictions to the PCSK9 inhibitor, while Amgen agreed to pay a full refund if treatment did not live up to the expectation of reducing heart attack and strokes in patients. *(Also see "Amgen's Repatha Contract With Harvard Pilgrim Includes A Full Refund" - Scrip, 3 May, 2017.)*

The market access group at AstraZeneca keeps outcomes-based reimbursement work separate from the traditional market access group, according to Suarez. In some instances, an outcomes-based contract can provide a foot in the door for a drug that might not have a preferred formulary position.

AstraZeneca has also experimented with offering a full refund if a medicine does not work as promised in one example, for the lung cancer drug *Iressa* (gefitinib). In an arrangement with **Express Scripts Holding Co.**, AstraZeneca agreed to refund the cost of the drug if it was discontinued before the third refill for any reason, including patient non-response.

"These are just not easy plug and play outcomes-based agreements that you can do anywhere," he said. "it does require a lot of partnership and collaboration between pharma and the insurers and the providers."

Having signed so many outcomes-based reimbursement contracts over the past few years, Suarez said AstraZeneca has learned a few lessons about the challenges.

"These are just not easy plug and play outcomes-based agreements that you can do anywhere," he said. "it does require a lot of partnership and collaboration between pharma and the insurers and the providers."

"It does require us to understand some of the limitations that exist within a payers data," he added. "Each one requires tailoring and collaboration."

US sales expectations for Brilinta have been challenged by competition from generic clopidogrel, which has led to pricing pressure from payers. The company noted in its April 27 first quarter earnings report that sales goals in the US for Brilinta have been "subdued" as a result of "affordability programs and managed care access."

Nevertheless, first quarter US sales for Brilinta rose 24% to $87m after increasing 45% for 2016 to $348m, in part due a positive impact from updated preferred guidelines from the American College of Cardiology and the American Heart Association.

US sales for Bydureon declined 4% to $463m in 2016, reflecting the impact of price concessions to payers, the company said. First quarter sales reached $127m in the US, ahead 18% compared to the previous year period

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FDA Tussles With Combination Products, Fires Up Oncology Center Of Excellence

By Brenda Sandburg

Photo by Brenda Sandburg

John Weiner, Tamy Kim, Paul Kluetz, Angela Krueger, Douglas Throckmorton, Peter Marks

FDA is struggling to come up with a solution to deal with complex combination products and has not ruled out a potential legislative fix.

FDA officials highlighted the challenges of dealing with these products during a panel discussion at the Drug Information Association's annual meeting in Chicago June 22.

The law and FDA regulations "never envisioned some of the products that we are starting to see or some of the complexities we are starting to see, such as a biologic administered with a device where the device that's used to administer that biologic could actually physically transform that biologic so that it has a different activity," said Center for Biologics Evaluation and Research Director Peter Marks.

"How you actually start to work with these things, whether you take cross labeling pathways or have some other type of combination pathway that you follow gets to be complicated," he said.

Marks also pointed to the complications manufacturers face as device makers want to use drugs that don't belong to them and a drug or biologic manufacturer must label their product for use with a device. He noted that the agency's Combination Products Policy Council is trying to work toward a solution, adding that he does not know if a proposed legislative fix will be needed.

FDA formed the Combination Products Policy Council in April 2016 to have a senior-level group deal with cross-cutting combination policy issues. In August, the agency also initiated an intercenter consult request pilot program, which includes deadlines for an office to complete and issue a consult on a combination product. *(Also see "FDA's Combo Products Review Transformation Begins" - Pink Sheet, 24 Aug, 2016.)*

The 21st Century Cures Act also included provisions on combination products. The statute established mandatory meetings between FDA and combination product developers and clarified the process for resolving disputes between FDA product centers.

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Douglas Throckmorton, deputy director of regulatory programs in the Center for Drug Evaluation and Research, said there are both cultural and legal complexities around this issue. He noted that historically, centers could take care of combination products like metered dose inhalers on their own.

"Now that the stakes have become more complicated we don't have that luxury. We've got to make sure that the standards CDRH [Center for Devices and Radiological Health] has for the device are applied appropriately for the combination product. So, a new different kind of coordination needs to happen," he said.

Will Centers Be Restructured?

Panelists also discussed the activities of the Oncology Center of Excellence (OCE), which was established in January in response to the 21st Century Cures Act. The legislation requires FDA to create cross-center groupings to coordinate handling of major diseases.

Paul Kluetz, OCE's acting associate director of patient outcomes, said one of the reasons the oncology center was formed is because the agency was already addressing the issues it is to tackle. He noted that in vitro diagnostic-drug combinations are very common and there is now potential for a combination of an in vitro diagnostic, therapeutic device and a drug or biologic product.

"My guess would be for the next OCE you want to look at a therapeutic area that already has a lot of combination product activity," that is exciting, is where science is headed, and is needed, he said.

Kluetz rattled off several things that the Oncology Center of Excellence is focusing on. In the area of real-world data, he said the center is investigating how to develop synthetic control arms to help with targeted populations that are difficult to randomize because they are so small. "We would like to understand how to create endpoints out of real-world data so that we can take real-world data and understand it enough to make it into real-world evidence that we can use for regulatory decision-making," he said.

OCE is also looking at pediatric drug development and the development of pediatric clinical outcome assessment tools. Kleutz noted that children sometimes cannot provide patient reported outcomes so there is a need to find other ways to get their perspective. The center is also seeking to aggregate and standardize FDA's clinical trial data sets and to set up a patient-focused development program.

Photo by Brenda Sandburg

Peter Marks, Director, Center for Biologics Evaluation and Research

Photo by Brenda Sandburg

Douglas Throckmorton, Deputy Director for Regulatory Programs, Center for Drug Evaluation and Research

Moderator John Weiner, associate director for policy in the Office of Combination Products, questioned if there should be a paradigm shift given the more complicated products coming into the agency. "Is the Center for Excellence enough? Are the Centers here for the long term?" he asked.

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Marks replied that they would have to see how things evolve over time. He said that while medical products are getting more complicated, at least for now "we can say there might be a need for buckets." He noted that CDRH has experts in engineering issues that impact most devices, while CDER has expertise in small molecule and protein drugs and CBER has expertise in gene and cell-based therapies, manufacturing challenges, and vaccines.

But Throckmorton indicated that the new complex products represent a small portion of the agency's workload. "If you pull back to a million feet, 90 plus percent of business Centers do does not touch this world," he said.

Promoting Industry Collaboration

A member of the audience noted that drug and device manufacturers that work together on a product are not always a good match and suggested that FDA give companies advice on who to partner with.

Weiner noted that this issue comes up quite a bit and asked the panelists for their views. Throckmorton said that CDER and CDRH have at times worked together to get trials conducted in specific areas but that it would be much harder to work together on product development. For example, he cited his experience in the opioid space where companies have been required to work together to develop Risk Evaluation and Mitigation Strategies.

"I would be telling a fib if I told you that convincing them to work together has been without its challenges," Throckmorton said.

Kluetz noted that some of his group's biggest successes have been getting competitors to come to consensus on a topic at a public workshop. He referred to an Oncologic Drugs Advisory Committee meeting on development of products to treat patients with non-metastatic castration-resistant prostate cancer. He said the meeting, which was held in 2011, led to the establishment of a special protocol assessment and critical drug development processes. Kluetz said the agency is probably going to hold a workshop on real-world data.

Tamy Kim, associate director for regulatory affairs, Office of Hematology & Oncology Products in the Office of New Drugs, agreed that workshops have been beneficial in getting industry to collaborate. She noted that the agency held a safety reporting workshop in conjunction with the American Society of Clinical Oncology's recent annual meeting to increase awareness of how industry should be using safety reports.

Kim said one company did an outstanding job and shared its best practices with other companies. She said the company was willing to do so because it realized the submission of safety reports to FDA was also affecting institutional review boards.

A representative from **Janssen Pharmaceutical Cos.** asked what FDA is doing in response to President Trump's executive order requiring that two regulations be eliminated for every new one issued. She noted that the White House has asked trade groups for information on this issue and they have been trying to come up with lists of guidances or other regulations that could either be eliminated or modified.

The Office of Management and Budget issued a memo that the order only applies to what are defined as significant regulations, meaning those that would have an annual adverse effect on the economy of $100m or more. *(Also see "US FDA Likely Not 'Significant', Could Be Mostly Spared From Trump's Regulation-Slashing Order" - Pink Sheet, 10 Feb, 2017.)*

Marks said the agency must interpret what a "significant effect" on industry means. "So, it's been a process of teasing this out," he said. He added that any guidance that need to get out because of public health concerns will get out.

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PDUFA VI: 'Building Trust' Is Theme Of FDA-Industry Negotiations

By Brenda Sandburg

Photo by Brenda Sandburg

Kim Quaintance-Lunn, VP and Head, US Regulatory Policy, Bayer; Theresa Mullin, Director, Office of Strategic Programs, CDER; Patrick Frey, Chief of Staff, Office of New Drugs, CDER; Sandra Milligan, Senior VP, Head of Global Regulatory Affairs and Clinical Safety, Merck Research Laboratories; Lucy Vereshchagina, Deputy VP, Science and Regulatory Advocacy, Pharmaceutical Research and Manufacturers of America

For FDA, the sixth authorization of the Prescription Drug User Fee Agreement (PDUFA VI) marks a positive shift in the relationship between the agency and industry.

"When I think about PDUFA V and then into PDUFA VI, the theme I feel like we've engaged in is in terms of breaking down barriers and building trust between FDA and industry," said Patrick Frey, chief of staff, Office of New Drugs in FDA's Center for Drug Evaluation and Research.

Speaking at the Drug Information Association's annual meeting in Chicago June 19, Frey noted that going into PDUFA V, both industry and agency were skeptical of each other. Industry wasn't sure that giving FDA a longer initial deadline could result in smoother reviews overall, and FDA was "worried about telling a company more about what was going on in our review process regarding the application, and if we were delivering bad news that was going to lead to an information dump on us to try to convince us otherwise."

But Frey said PDUFA V was implemented successfully and there ended up being "very good dialogues with industry" about problems with applications and the path forward.

PDUFA VI is now on track to be implemented in the fall after Congress reauthorizes the agency's user fee programs.

Focus On Drug Development Cycle

Sandra Milligan, senior VP, head of global regulatory affairs and clinical safety at **Merck Research Laboratories**, was involved in PDUFA VI negotiations, which she characterized as "amazing." She said that from an industry perspective, the discussions involved a shift away from trying to speed up the drug review process to focusing on the drug development cycle.

"We took a look at PDUFA I through V and we didn't see a need to squeeze more time out of the review process," Milligan said. The focus "was more about how can we collaborate and think differently about shortening the development cycle."

She also gave "hats off to FDA" for their accomplishments in hiring scientists and project managers and moving efficiently through submissions. "We've seen they can step up even faster with some of the accelerated review mechanisms like the breakthrough designation," she added.

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Frey noted that there has been an increase in meeting requests year over year with 3,200 to 3,300 requests in fiscal year 2016, 85% of which are sought with CDER. He said the agency honors about 95% of meeting requests either through face to face meetings, preliminary responses or a written response only.

The agency recognized the need for breathing room and changed its target for scheduling type A and C meetings. The moderator, Kim Quaintance-Lunn, VP and head of US regulatory policy at **Bayer AG**, asked what industry got out of giving FDA breathing space.

Milligan replied that sponsors are willing to provide a few more days for review to make sure reviewers have enough time so when they get face-to-face meetings or a teleconference or written response they are well prepared. We are "making sure we have high quality dialogues with the agency instead of a rush toward the timeline," she said.

Pilot Programs Offer 'Amazing Opportunity'

FDA's Theresa Mullin, director of the Office of Strategic Programs in CDER, noted the proposed enhancements in PDUFA VI, which include a new end of phase type B meeting and the establishment of a new user fee structure in which there is both an application fee and program fee.

Milligan said the aspect of PDUFA VI that she finds the most exciting are the two pilot projects that were proposed and agreed to, a model-informed drug development program and a program for highly innovative trial designs. For sponsors who participate in the pilots, FDA will grant a pair of meetings, an initial meeting and a follow-up 120 days later.

This is "an amazing opportunity for a company to step forward or a small number of companies to step forward" and engage in a pilot and share their experiences so we can all learn, Milligan said.

Photo by Brenda Sandburg

Patrick Frey, Chief of Staff, Office of New Drugs, Center for Drug Evaluation and Research

Photo by Brenda Sandburg

Sandra Milligan, Senior VP, Head of Global Regulatory Affairs and Clincial Safety, Merck Research Laboratories

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Generic Program Is Biggest Extra Item In Senate User Fee Reauthorization Bill

By M. Nielsen Hobbs

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The US Congressional Budget Office (CBO) has concluded that FDA would need additional resources beyond user fees to carry out all the programs envisioned in the Senate's user fee reauthorization bill, with activities related to generic drugs accounting for much of them.

CBO's score estimates that, "assuming appropriation actions consistent with the bill," FDA would spend an additional $1.24 bil. over the next five years – $566 mil. of which would be spent on generic drug activities. The budget office classifies another $105 mil. for FDA "to issue product specific guidance on establishing bioequivalence to complex drugs that are not biological products" in the "miscellaneous" category but those efforts also seem like they may have great value for ANDA sponsors.

S. 934, called the FDA Reauthorization Act, would require to give priority review to ANDAs for products where there are three or fewer applications. "Based on an analysis of information from FDA, CBO estimates that implementing those provisions would require about 500 additional full-time-equivalent (FTE) positions by 2022 (at an average annual cost of about $300,000 per FTE) and additional funding totaling $14 million per year, on average, to carry out a variety of activities related to information technology."

In total, the spending would include:

- $385 million to expand the types of generic applicants to which FDA must grant priority review and to provide technical assistance to such applicants;
- $102 million to collect information about generic drugs with three or fewer competitors and to build the necessary information technology infrastructure to gather and publish this information biannually;

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- $69 million to re-inspect generic drug manufacturing facilities, in certain instances, if they had a known deficiency that was remedied by the manufacturer; and
- $10 million to collect and publish information about the status of generic drug applications.

If FDA follows the spirit of the law and not just the letter, the resource need would be even higher, CBO notes.

"Title IX also would express the sense of the Senate that FDA should respond to suitability petitions within 90 days of submission. (Generic drug manufacturers submit suitability petitions to FDA when they would like to submit an application for a product that has a different manner of administration, dosage form, or strength than drugs with the same active ingredient that are currently on the market.) CBO estimates that there would be no budgetary effects from that provision because the bill does not require FDA to follow the 90-day guideline. However, based on information from FDA, CBO expects if FDA did follow that guideline, costs would increase by about $20 million over the 2018-2022 period."

CBO's estimate also serve to underscore the strain that FDA might feel as it develops non-statutory initiatives to encourage and accelerate generic applications. Commissioner Scott Gottlieb has emphasized generic approvals as an area where FDA can make an impact on drug pricing. *(Also see "Gottlieb Places Drug Pricing Out Front In First Speech To US FDA Staff" - Pink Sheet, 16 May, 2017.)*

User fee legislation has cleared committees in the House and the Senate, but has yet to come to the floor in either chamber. The bills need to pass, be reconciled and signed by the President before the end of July or FDA may be forced to send layoff notices to user-fee supported staff.

Perhaps the most serious conclusion by CBO is the estimate that the Senate legislation would increase budget deficits by $15 million during the next ten years. That's actually a small amount money in Washington, but it is enough to block movement of the bill under Congressional rules. Last year's FDA reform legislation, the 21st Century Cures Act, also faced a challenge finding an acceptable "pay-for" to offset its increased spending, and the CBO score could fuel some unpleasant fights for the biopharma industry to keep undesired cost saving measures out of the user fee bill – anything from explicit price controls to REMS changes that would allow faster generic access.

Such fights will of course be worth it for pharma, but it's one of the cruel ironies that a "clean" bill – which doesn't include much in the way of pharma-positive reforms aside from renewing the user fee program itself – will nevertheless likely require a great deal of industry support and engagement. The effort won't be to shape something positive, though companies are excited about PDUFA VI, but instead to prevent something bad from being enacted.

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Medpace Celebrates 25 Years 1992-2017

This year, Medpace marks its 25th year as a company. Founded in July, 1992 by Dr. August J. Troendle, Medpace has grown from a small group of dedicated people looking for a better way to conduct clinical research to a publicly-held, global community of 2,500 employees.

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REAL-WORLD EVIDENCE: Between 'Nirvana' And Electronic Roadblocks

By Brenda Sandburg

The biggest block to the pharmaceutical industry using real-world evidence for regulatory purposes is the inadequate data in electronic health records (EHR), according to FDA's Jonathan Jarow, senior medical advisor to the director of the Center for Drug Evaluation and Research.

"The traditional outcome measures that are used in traditional drug development aren't in the EHR," Jarow said. "Right now, it's going to be tough to do what everyone wants to do until that data is there."

Who is going to make that happen? It will be up to industry to influence EHR systems so they include endpoints of interest, such as depression and pain scores, Jarrow said. If the pharmaceutical industry feels it "can get outcomes and get past regulatory hurdles" it will invest in this and partner with health care systems, he stated.

Jarow spoke on a panel about real-world data and real-world evidence for assessing efficacy and effectiveness at the Drug Information Association's annual meeting in Chicago June 21.

"Real-world evidence has become the sexy term of the year," he said.

He noted that FDA defines real-world evidence as evidence generated from real-world data in a highly pragmatic fashion. "Most people think that I could have someone in my IT department push a button on the computer with an existing data set and find evidence that my drug is effective for a new indication and then submit that to FDA and get approval," he said. "That's what I think is behind a lot of excitement about real-world evidence. I'm not saying that it's impossible, but it's going to be difficult."

What's Needed For 'Nirvana'

Jarow described what would be "nirvana" for use of real-world evidence. The first thing would be to have a universal identifier for every U.S. citizen, he said. But he noted that since US law does not allow the government to assign unique identifiers, it must come from the private sector if it is going to happen.

Photo by Brenda Sandburg

FDA's Jonathan Jarow, senior medical advisor to the director of the Center for Drug Evaluation and Research

The other things on his list include a standardized data structure; complete linkage of data between hospitals, pharmacies, outpatient clinics, social media and death registries; and open access with consent for full use of de-identified data. He said Sweden has all these features.

Jarow noted that while the focus is on using real-world evidence to get regulatory approval of drug applications, it can also be used for clinical practice guidelines to decide how to best manage patients, for payers deciding whether to pay for a drug, and for comparative effectiveness.

Real-world data and evidence can also be used in developing randomized controlled trials, he said, noting that it can be useful in selecting study sites that are likely to have the patients of interest, can generate adverse event reporting and be used for endpoint ascertainment.

Jarow cited several drugs that have been approved with real-world data, including **Wellstat Therapeutics Corp.**'s *Vistogard* (uridine triacetate) for treatment of overdoses of the cancer medicines fluorouracil or capecitabine.

"It's pretty rare. We're not doing this for a standard diabetic drug or hypertension or hypercholesterolemic drug. But there is potential for incorporation of real-world evidence both in the development of a drug and certainly in the post-market evaluation of a drug," Jarow said.

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REAL-WORLD EVIDENCE:
'Hot Topic' At US FDA, But Not On Front Burner

By Michael McCaughan

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Real-world evidence is definitely a "hot topic" at FDA.

That phrase was used twice in one week by two different drug review officials from two different divisions in two very different contexts to describe the concept of applying evidence derived from actual use of medicines to enhance regulatory decisions:

- The first was Division of Bone, Reproductive and Urologic Products Director Hylton Joffee during a Dec. 6 advisory committee discussion of clinical trial endpoints for non-testosterone therapies for hypogonadism.
- The second was from Office of Hematology & Oncology Products Lead Medical Officer Gideon Blumenthal during a Dec. 13 National Academies of Medicine workshop on the drug development paradigm in oncology.

The shared use of the phrase "hot topic" also reflected a broader shared message from the agency in the context of those two events: as eager as many inside and outside of FDA are to expand the boundaries for evidence collection to support regulatory decisions, there is still a ways to go before that will happen. Real-world evidence, in other words, isn't a regulatory reality just yet.

During the advisory committee meeting, the role of "real-world evidence" was not central to the discussion by FDA or the committee. Fundamentally, the panel provided support for FDA's view that non-testosterone therapies should be held to same (relatively new) standard applied for testosterone agents: any indications for use in the "Low T" population should be supported be evidence of clinical benefit – not just elevated testosterone levels. *(Also see "Hypogonadism Trial Designs: FDA Panel Favors Symptom Assessments, Fertility Measures" - Pink Sheet, 6 Dec, 2016.)*

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That means, most likely, a multi-year process to develop appropriate endpoints – including patient reported outcomes – and then confirm benefit in pivotal studies. *(Also see "FDA's Tough Stance On Patient-Reported Outcomes Underscored At Repros Meeting" - Pink Sheet, 7 Dec, 2016.)*

But an exchange on the potential role of real-world evidence may point to a very different approach to developing evidence in cases of broad off-label use in the future – and to different levels of enthusiasm for doing so in industry and within FDA.

The subject was raised by the industry representative on the committee, Bayer VP Gerard Nahum. In the context of proposed trial designs, he asked Joffe, what role might "real-world evidence" have to "supplement the label and augment the indications?"

> **Real-world evidence is "a real opportunity," but it has a "longer horizon for its greatest payoff than its proponents think." – CDER Director Janet Woodcock**

Joffe responded by acknowledging that "real-world evidence is a hot topic these days," and stressing that the agency is "always open to hearing proposals if companies have ideas on how to leverage data."

However, he added, "the devils are in the detail. How good is the evidence? What exactly is it showing?" He noted the prior discussion of published studies using unvalidated PROs as an example of what might look like strong "real-world evidence" that may not be interpretable in practice. So discussing the role of real-world evidence in this context, Joffe said, "is hard in the abstract."

'Stop Talking About It And Start Doing It'

The discussion of real-world evidence (RWE) in the role of oncology development was more literally part of the agenda at the National Academies of Medicine (NAM) event, but FDA's message was essentially the same.

In his presentation on FDA's willingness to accept non-randomized trials in the context of extremely large effect sizes for oncology drugs, Blumenthal listed a number of considerations, including "Can RWE play a role for post-marketing studies?" That issue, Blumenthal added, is a "very hot topic" at FDA.

However, as Center for Drug Evaluation & Research Director Janet Woodcock made clear during introductory remarks at the NAM conference Dec. 12, while RWE is "a real opportunity," it has a "longer horizon for its greatest payoff than its proponents think." And there is never "going to be a button we can push and get answers."

Woodcock has been playing the role of curbing enthusiasm for RWE in a number of different settings. During a November Prevision Policy/Friends of Cancer Research conference, she pointedly noted that, for all the projects fleshing out RWE under way inside FDA and outside, the exact state of the effort "is still a bit of a mystery to me." *(Also see "FDA/CMS Collaboration: "Sleeper Group" Goes Public With Call For Real-World Evidence" - Pink Sheet, 9 Nov, 2016.)*

That message has apparently been delivered directly to some of the leading advocates for the approach in academia. During the NAM meeting, Harvard Pilgrim's Jeffrey Brown – who has worked with Richard Platt on the FDA Sentinel Initiative – began his by citing recent meeting he had with FDA Commissioner Robert Califf. According to Brown, the commissioner told him, bluntly, "Stop talking about it and start doing it."

Woodcock's more pointed comments Dec. 12 also reflected a sensitivity to critics of the just-signed 21st Century Cures Act, who point to relatively open-ended provision on RWE as evidence that the law will undermine patient safety. FOCR Founder Ellen Sigal followed Woodcock's opening remarks by more directly noting that fear: "So I shouldn't believe everything I read in the press about Real-world Evidence?" she joked.

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EMA, FDA Talk Real-world Evidence, Mutual Recognition, Generic Drugs

By Brenda Sandburg

Photo by Brenda Sandburg

Alison Cave, Peter Marks, Jarilyn Dupont, Juan García-Burgos, Sandra Kweder, Sabine Haubenreisser, Anabela Marcal, Dara Corrigan, Sarah Pope Milksinski, Agnès Saint Raymond

US FDA and the European Medicines Agency may expand their collaboration to include such topics as generic drug reviews and good clinical practices.

Officials from the two regulatory bodies participated in a panel devoted to answering industry questions at the Drug Information Association's annual meeting in Chicago June 22. Audience members asked about the Mutual Recognition Agreement, which will enable FDA and the European Union to rely on each other's good manufacturing practice (GMP) inspections. The agreement was signed by US and EU officials in January and March, respectively. *(Also see "EU, US Finally Agree On Mutual Recognition Of GMP Inspections" - , 2 Mar, 2017.)*

The audience applauded when Dara Corrigan, FDA acting deputy commissioner for global regulatory operations and policy, described the agreement as "an historic moment" for FDA. Corrigan noted that an initial agreement had been signed in 1998 but never implemented. To finalize the deal, FDA had to be able to show that it used the same procedure to evaluate the capabilities of the 28-member EU states, which have their own pharmaceutical inspectorates.

In the last few years, 40% to 43% of FDA's inspections have been conducted in the EU, and the agreement will now enable the agency to "allocate scarce resources to areas of greater risk," Corrigan said.

A representative of **Novo Nordisk AS** asked if the agencies had discussed expanding the agreement beyond GMP to good clinical practice (GCP) and good operating practice (GOP). Anabela Marcal, head of compliance and inspections at EMA, said that even though there is no agreement on GCP, the two agencies collaborate closely and since 2009 have regularly exchanged information on applications.

Marcal said EMA does not have the resources to inspect all clinical trial sites. "If FDA already has inspected a site and everything was okay and there was no major problem, in general we would not go and inspect that specific site," she stated.

Possible Collaboration On Complex Generics

A representative from **Mylan NV** asked the panelists for their views about collaboration on generic drug reviews.

FDA's Sandra Kweder, deputy director, liaison to the EMA, Office of International Programs, responded that the agencies do not currently have ongoing interactions on generic drugs, noting that they are not included in the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. But she said there is interest in having discussions like those they've had about biosimilars.

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Sabine Haubenreisser, EMA's liaison to FDA, said that regarding biosimilars, the two agencies came to an agreement on use of studies with one reference product to avoid duplication and on the application of bridging data. "We are engaging in discussion as well on how we could do this for complex generics," Haubenreisser said. She added that the two agencies are considering whether they can find a common definition and sourcing data.

Clear Endpoints, Registry Data Bolster Real-World Evidence

In opening comments, Center for Biologics Evaluation and Research Director Peter Marks discussed why real-world evidence has gained so much attention. He noted the limitations of randomized clinical trials, which he said are very good at showing an effect between two groups that are very well defined. But in other instances, such as cancer trials, people with abnormal kidney or abnormal liver function may be excluded so the trial may support superiority of one drug over another but not in a patient population that is relevant for the largest number of people.

"If you used real-world evidence, you could have looser exclusion criteria or look at a greater variety of people in trials," Marks said.

In addition, he noted that real-world evidence may be used to significantly reduce the cost of Phase III testing by using large databases with patient information. Marks said one could potentially collect data in databases and use it to modify the label, to get historical control data, and for safety surveillance.

Alison Cave, principal scientific administrator at EMA, noted that some of the challenges with real-world evidence include how complete and valid the data is, and the different views about the meaning of data quality.

As to when real-world data can be used, she said it will depend on several factors: the context of its use; the stage of the product for which the data will be used; the questions being asked of the data and the weight being placed on the data; the context of other evidence; the disease severity; the availability of other treatment options; the prevalence of the condition; and the outcome that's going to be assessed.

A representative from **Ironwood Pharmaceuticals Inc.** asked for examples in which EMA has used real-world evidence in its regulatory decision making.

Photo by Brenda Sandburg

Sandra Kweder, Deputy Director, Liaison to The EMA, Office of International Programs

Cave cited two instances in which EMA used real-world data to support an authorization. One case involved a cell-based therapy product, **MolMed SpA**'s *Zalmoxis*, which had shown success in a Phase I/II trial. The treatment had a clear endpoint and investigators used data from a European transplant registry to provide a control group to an ongoing randomized controlled trial and were thus able to obtain conditional marketing authorization as adjunctive treatment in haploidentical haemotopoietic stem cell transplantation of adults with high-risk haematological malignancies.

Another case involved **Alexion Pharmaceuticals Inc.**'s *Soliris* (eculizumab), a drug that was initially restricted to use in patients with a certain disease severity. Investigators used a disease registry to obtain a comparator group to measure efficacy of the treated group and based on this data obtained an extension of the drug indication. EMA initially approved Soliris for the treatment of paroxysmal nocturnal hemoglobinuria.

"One take home message is that not all endpoints are going to be suitable. But where the outcome can be clearly captured, then that offers an opportunity," Cave said. "The second point is that when progression of the disease is well known, possibly from real-world data," you can clearly target your patient population.

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Breakthrough Designation's Predictive Value Reinforced By R&D Success Rates Analysis

By Patricia Reilly

Biopharma candidates that earned a US FDA designation as a potential "breakthrough" product were more than twice as likely to move from Phase I to Phase II and from Phase II to Phase III compared to candidates with certain other special designations, according to a recent analysis of drug development data tracked in Biomedtracker.

There was nearly as great a difference in moving from Phase III to submission of a new drug application or biologics license application in the US. The results underscore that FDA's high-bar selection process has translated into focusing breakthrough designations on products likely to reach the market.

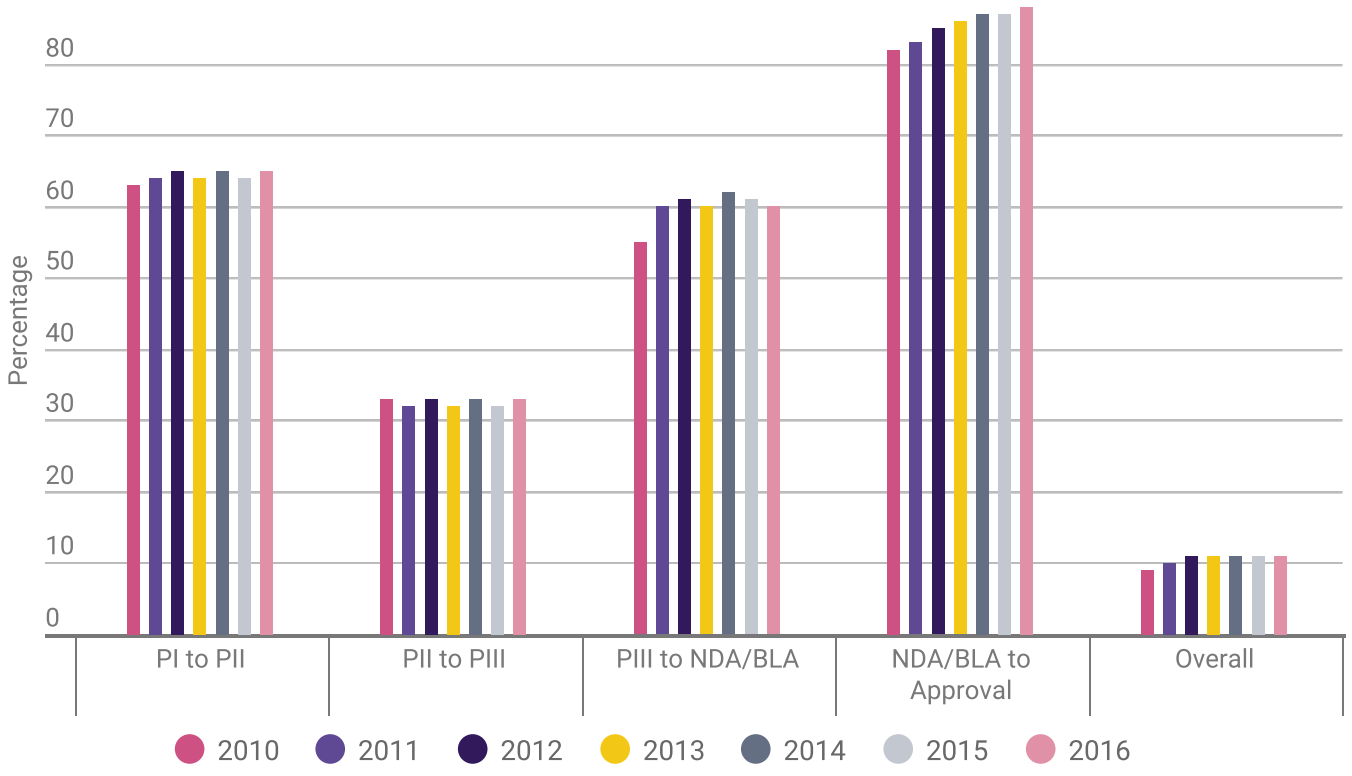
The data analysis provides perspective on the success rates of all drugs (new molecular entities, non-NMEs, and biologics) moving through clinical trials between 2010 and 2016. The latest results are consistent with BMT findings from previous years in terms of success and attrition rates by clinical phase, success rates by molecule type, success rates by therapeutic area and for all drugs versus drugs with special designations (special protocol assessment, orphan, breakthrough and fast track).

Overall success rates for products tracked from Phase I to FDA approval remained at 11%, and have remained roughly the same since 2012. The study found attrition rates in Phase II continue to be the highest of any phase of development, which has been seen in other similar studies.

Success rates in each clinical phase rose slightly from 2015 to 2016 except for Phase III to NDA/BLA (*see chart*).

The analysis also examined success rates by phase for different types of molecules – small-molecule NMEs, non-NMEs

Success Rates By Phase (lead and secondary indications), 2010-2016



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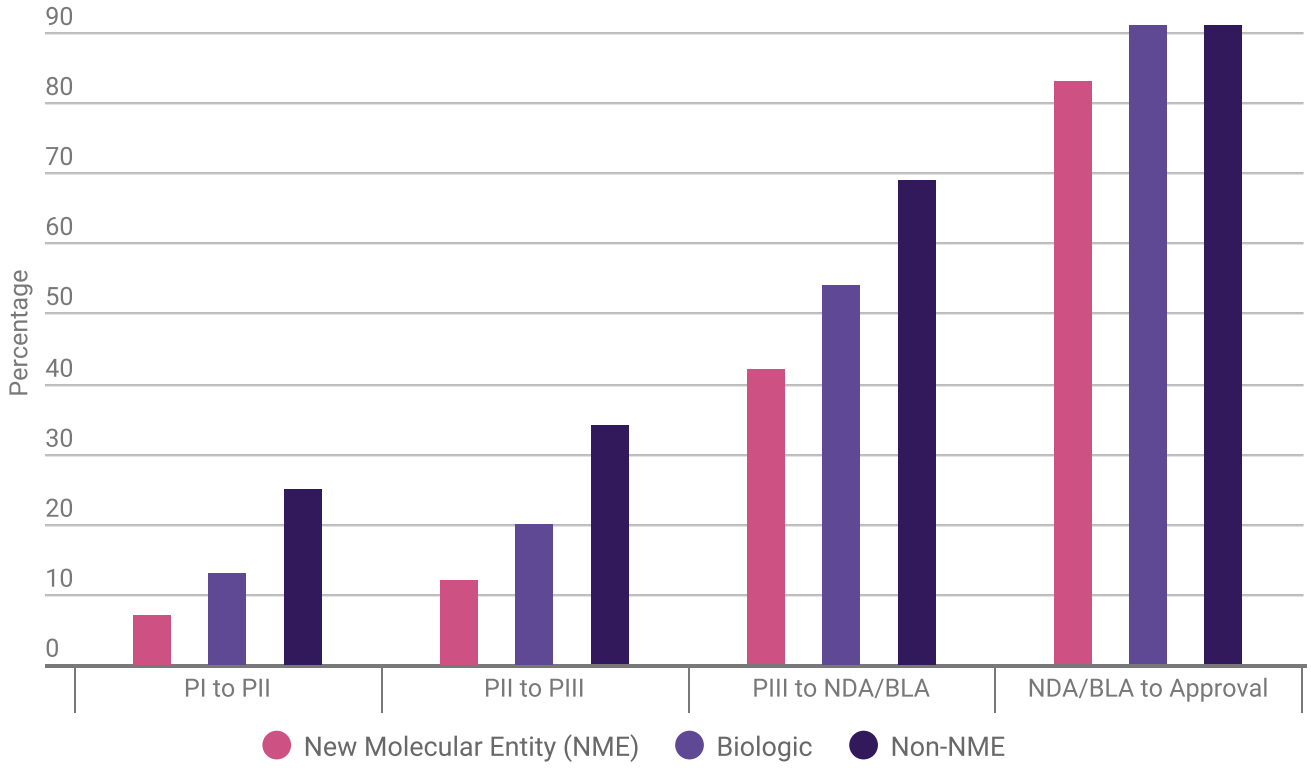
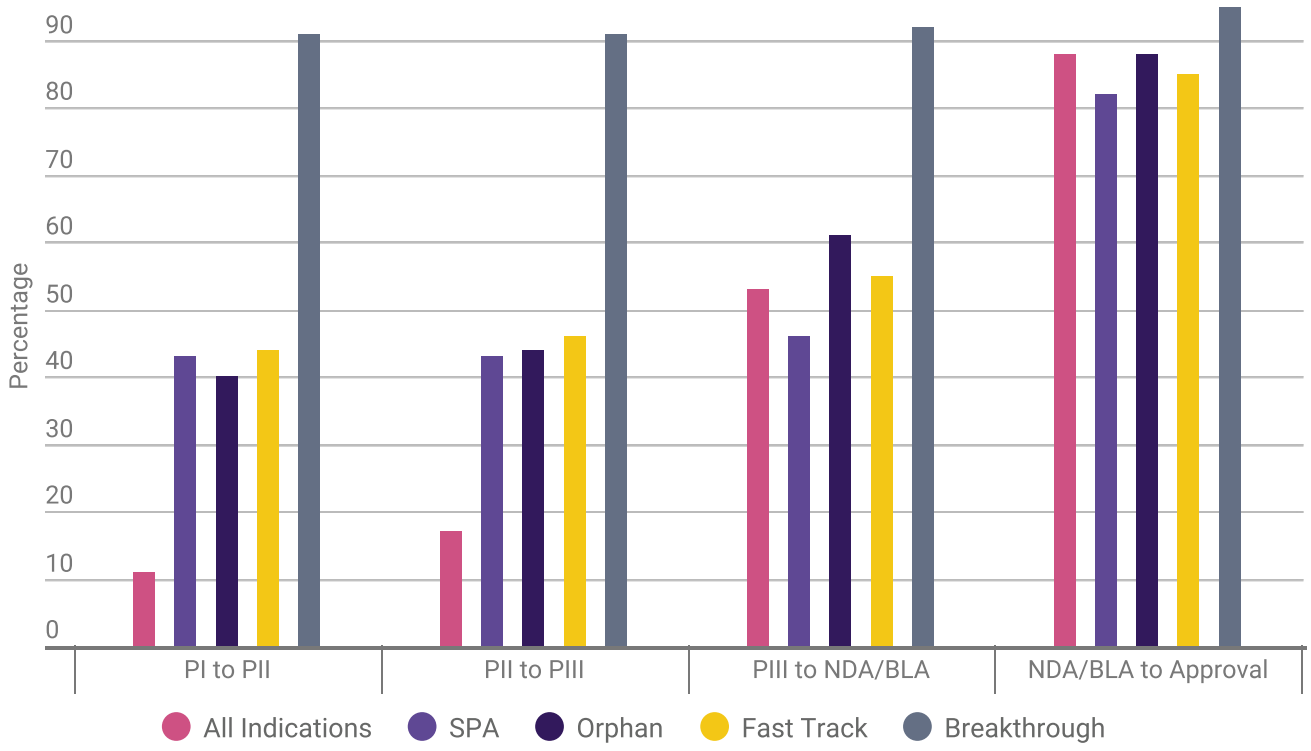
Success Rates By Molecule Type, 2010-2016



Trial Phases And NDA/BLA Success Rates, 2010-2016, By Designation



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and biologics (*see chart, top of p. 21*). In three of the phases examined (Phase I to Phase II, II to III, and III to NDA/BLA), the non-NMEs had the highest success rates. However, in the NDA/BLA to approval phase, non-NMEs and Biologics had the same success rates. NMEs consistently had the lowest success rates, which mirrors the results from our previous studies.

The 2017 study found that breakthrough designation drugs had the highest late-phase success rates when compared to all drugs, orphan drugs, fast track and products with special protocol assessment (SPA). In the Phase III to NDA/BLA transition, SPA drugs had the lowest success rate, and this trend continued until the NDA/BLA to approval transition.

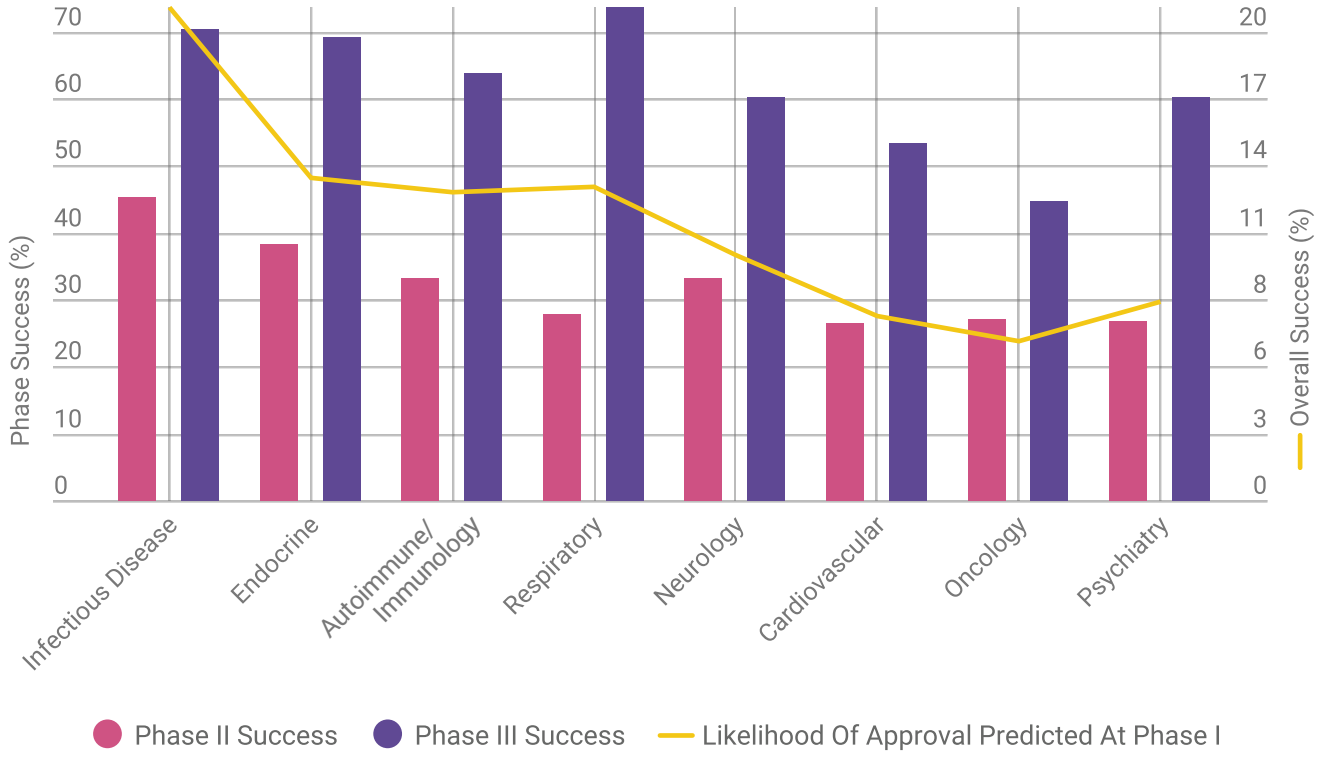
A likely reason why the BTD group has such a high success rate could point to the difficulty in earning this designation. While FDA has never outlined detailed criteria for qualifying for BTD, the bar is set very high and as such, it's almost a guarantee for approval, so long as the pivotal trial is a success. FDA reported that for fiscal year 2016, of the 106 requests for BTD only 46 were granted, 48 denied, and 12 withdrawn. Looking historically over the past four years, an average of only 36% of requests were granted this breakthrough status. It's therefore not surprising that breakthrough status allows for much quicker approval than other pathways.

Regarding the obvious lag between orphan and BTD success rates, most BTDs tend to be orphan, but not vice versa. Orphan designations are relatively easy to come by and don't include the same amount of regulatory scrutiny, which results in a higher n-value and higher failure rate (*see chart, bottom of p. 21*).

Looking at success rates based on therapeutic area, while Infectious diseases have the highest Phase II success rate, respiratory products moved ahead in Phase III in the latest evaluation. And although oncology has the greatest number of products in clinical trials, the success rates were similar to other therapeutic areas in Phase II but consistently lower in Phase III (*see chart, below*).

[Editor's note: Biomedtracker provides in-depth tracking of the key milestones in drug development and projections of likelihood of regulatory approval.]

Success Rates At Phase II And Phase III By Therapeutic Area, 2010-2016



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Social Media Trends DIA 2017

8021 TOTAL POSTS:

- **3725** tweets
- **4047** shares/retweets
- **249** comments

TWEETS CLASSIFIED BY TOPIC AREAS:

- Big data/ehealth/ innovation **942**
- Medical affairs **363**
- Regulatory **333**
- Preclinical/clinical **316**
- Patient engagement **295**

Zach Brennan
@ZacharyBrennan Jun 20

FDA's Christl says we may see interchangeable biosimilars approved in next 2 years #DIA2017

2 9 7

Savvy Cooperative
@savvy_coop Jun 20

Need more than #mhealth & #digitalhealth data. The #PatientExperience is more than just numbers. Need #patientvoice to explain data #DIA2017

6 6

Kosmas Kretsos
@kkretsos Jun 21

Sincere, inspiring brainstorming at #DIA2017 on making #clinicaltrials better for #patients by @MySCRS @LillyTrials @Merck @pfizer...

1 6 4

Elizabeth Lincoln
@ElizLincoln Jun 21

Patient caregiver-collected #PRO data persuades FDA that drug was working!! @fundDuchenne #patientadvocacy #DIA2017

1 10

Kim McCleary
@KimTweetsDC Jun 20

Juan Garcia-Burgos @EMA_News: Expertise #patients bring to regulators is different from other KOLs but crucial. #patientengagement #DIA2017

5 4

JB Ashtin
@JBAshtin Jun 21

"...diversity in clin trials not about social equality but about what is right." We have a long way to go. @drjohnwhyte #DIA2017

4 4

POPULAR #s

#clinicaltrials
#digital
#pharmacovigilence
#drugsafety

Source: DIA's DIAlive tracking site June 18-22; twitter. DIALive tracks tweets by conference attendees, though some discussions may be on broader topics.

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