Patient Advocacy With FDA Review Staff Will Be Tougher Post-Sarepta

COLE WERBLE pinkeditor@informa.com

When FDA embarked on a more aggressive reaching out to patient advocacy groups in 2012, one of the frequently stated long-term objectives was to find a way to bring patients and the researchers involved with them into more direct contact with FDA drug reviewers.

The broad patient-focused scheduled meetings on diseases selected by FDA review divisions were intended as just one part of what was seen as an eventual effort to provide the resources of patients and researchers (as distinct from the commercial sponsor) to the FDA review staff.

The more interesting long-term projects were to find useful ways for patient advocacy groups to meet with review staff perhaps early in the development cycle to provide the reviewers with perspective on medical need and a close view of the disease state – especially in rare diseases with which FDA reviewers would be unlikely to have much professional or clinical understanding.

The experience of the Neurology Division with the review of Sarepta’s Exondys 51 (eteplirsen) is likely to be a major setback to that broader effort to increase the access for patients to scientific reviewers.

“Personal”, “intense” and “intimidating”: that is how one of the Neurology Division reviewers described the interactions with the Duchenne Muscular Dystrophy patient advocates. Two division staff departures were tied to the way the approval decision was handled, a key factor of which, from the review level perspective, was the relationship with the patient advocacy groups.

That type of characterization and inside-story from FDA staff on the Exondys 51 review threatens to become part of the common FDA review staff perception of patient advocates. If so, it will be much tougher for patient advocacy groups to get meetings – or more precisely, productive meetings – with FDA’s medical/review staff. The five-year effort to establish more connections and exchange between patients and FDA reviewers could experience a significant setback.

‘VULGAR’ COMMUNICATIONS

There are some review areas within FDA – primarily oncology – which have worked out productive mechanisms for meetings with the patient community and research communities. Those will probably not be affected by the Sarepta experience. The potential damage will be to those other review areas that were making the first steps towards paying more attention to patient commentary.

The characterizations of the DMD meet-
The balance of power behind the prescribing decision is changing: payers are ever more in charge. That means that insight into how payers make decisions – how they evaluate drugs, one against another – will be crucial to any successful drug launch.

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Jim O’Neill Is “Free For Global AMR Role” After Leaving UK Government
http://bit.ly/2cOCZhm
Having suddenly resigned from the UK government, Jim O’Neill says he’s now available to take on a global role, if asked, to promote concrete action on tackling antimicrobial resistance within promised timeframes.

Duke’s McClellan: Changing Drug Development Policy From Outside FDA
In an interview, Margolis Center for Health Policy’s Mark McClellan and Gregory Daniel talk about their recent move from Brookings to Duke, the breadth and impact of their work with FDA on drug development issues, and opportunities for potential future collaborations under PDUFA VI.

Biosimilars Will Get PDUFA-Style Reviews Under New User Fee Plan
http://bit.ly/2d9bZJ0
FDA will have a total of 12 months to review 351(k) applications and additional time to schedule certain product development meetings under the Biosimilar User Fee Act II agreement; measures to enhance management of user fee resources and improve hiring will carry over from PDUFA VI.

‘Right To Try’ Or ‘Right To Ask’? Hearing Spotlights Adverse Events As Key Barrier To Expanded Access
http://bit.ly/2cOD7xe
FDA and the pharmaceutical industry appear to have a shared interest in finding ways to dramatically increase expanded access programs to avoid a potentially difficult fight over ‘Right to Try’ legislation at the federal level in 2017. A September 22 hearing on a pending Senate bill illustrates why.

Priority Review Voucher Program For Rare Pediatric Diseases Extended As FDA Lowers Fee
http://bit.ly/2dx5oeB
Next fiscal year will be a good one to redeem a voucher, and probably to qualify for one as well.

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ings between staff and patient advocates in the unusual FDA approval memos documenting the scientific disputes also record the occasionally “vulgar” communications from outside FDA to the Neurology reviewers. That tone was also evident during the very public display of pressure on FDA at the April 25 Peripheral & Central Nervous System Advisory Committee discussion of the application.

Agency staff has become inured over decades to the open public hearing segment of advisory committees and even has begun in some cases to show more interest and empathy to that part of the committee review process. However, the Sarepta meeting was one of the more trying recent versions of public participation. It was a very inclusive process. FDA staff acknowledges the meeting was unusual for having almost every patient (all but one) in the key clinical trial directly involved or represented at the meeting. That is not a negative, just primarily a comment on the small size of the number of patients in the trials.

NEUROLOGY EXPERIENCE NOTICED THROUGHOUT FDA
Office of Drug Evaluation I Director Ellis Unger described that event in his memo recommending rejection of accelerated approval for the drug as a session where the “committee was under intense and near-incessant pressure from a large public audience, urging them to believe that eteplirsen was effective, and life changing in some circumstances. Emotions in the room ran high. In spite of this pressure, that majority of the Advisory Committee voted against both conventional and accelerated approval.”

The story of that difficult meeting spread quickly within review divisions at FDA as a sign of the return to high stress, high pressure public events. It crept into discussions among FDA reviewers at forums like training sessions in the weeks following the advisory committee. The Exondys 51 review was not an isolated event in the Neurology Division or ODEI; it reverberated throughout the new drug review operations.

Intense public input at advisory committees is not completely contrary to the public nature of the process; but, at the level of the Sarepta meeting and in conjunction with the other contacts to reviewers, it certainly fosters a potential “us-versus-them” undertone at the meetings and in contacts with patient advocates.

TESTIMONY VS. DATA
In his decision memo, Unger dispassionately notes that the patient testimonies at the advisory committee “were quite consistent and remarkably positive: all were convinced that eteplirsen had made a substantial positive impact on their physical performance, improving numerous aspects of their lives.” He contrasted the patient testimony on improvement in physical function against the lack of evidence of improvement in the data submitted from the pivotal study.

Future sponsors and patient advocacy groups that plan to bring arguments and perspective on drug development to the attention of FDA at the review division level should probably pay as much attention to Unger’s final assessment of the impact of patient input as to the unusual accelerated approval decision on Exondys 51.

“Patient-focused drug development is about listening to patient perspectives about what matters to them; it is not about basing drug approvals on anecdotal testimony that is not corroborated by data,” Unger stated.

AN ‘EVOLVING’ ART
FDA Commissioner Robert Califf referred to the threat to relations between patient groups and review staff in his decision to uphold Center for Drug Evaluation and Research Director Janet Woodcock’s approval of Exondys 51. He described the art of patient-centered drug development as “evolving” – a term that appears to emphasize the fragility of that approach.

Califf credits both Woodcock and Unger (who openly challenged Woodcock’s decision) for recognizing the “dynamic” of understanding the concerns of parents of very sick children and “the significant pressure on all involved.” That is putting the best face on two very different views of the value of patient advocacy and parental involvement in the review process.

Califf restated the long-term trend towards listening to the patient and the commitment of CDER to patient processes as a priority. “With a significant history dating back to the development of drugs for HIV/AIDS, patient-focused drug development is not an entirely new component of FDA’s regulatory process, and it remains an explicit CDER priority in the current era.”

The question is whether Woodcock can be as effective a proponent for that process in the wake of her role with Exondys 51 approval as she was when she re-committed the agency to patient orientation starting in advance of PDUFA V.

From the editors of the RPM Report.
Published online September 23, 2016
FDA’s Drug Promotion Advisory Reviews Taking Longer

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Biopharma companies can improve their chances of getting timely FDA feedback on core product launch promotional materials through high-quality submissions and close interactions with review staff, the head of the agency’s drug promotion review office said.

Tom Abrams, director of the Center for Drug Evaluation and Research’s Office of Prescription Drug Promotion (OPDP), acknowledged industry concerns that advisory reviews of core launch materials have been taking longer than expected but suggested steps industry can take to help move the process along.

Abrams’ comments at the Food and Drug Law Institute’s Advertising and Promotion Conference Sept. 27 in Washington, DC, that OPDP will continue to put its primary focus on activities, such as pre-launch advisory reviews, that encourage voluntary compliance with FDA’s drug promotion rules suggest that industry is unlikely to see a big increase in warning or untitled letters targeting violative promotions in the coming months.

**COMPLEX ISSUES REQUIRE MORE TIME**

Although FDA generally does not require prior approval of promotional materials, OPDP will provide comments on proposed advertisements and labeling pieces before use upon request.

OPDP’s internal goal is to provide advisory comments on draft core launch materials within 45 days, not including the time needed for a consultation with the medical review division, Abrams said.

“Until last year we were meeting that the majority of the time – over 90% of the time,” Abrams said. “However, some recent submissions have presented complex issues that require a deeper level of review, more consultation with our colleagues in other offices, and therefore [are] taking a longer period of time.”

Abrams sought to assure sponsors that launch materials are being actively reviewed. “It’s not like they’re on the back burner;” he said. “But they do take longer because there’s more review processes and digging down into these complex issues.”

Lisa Stockbridge, chief of the Center for Biologics Evaluation and Research’s Advertising and Promotional Labeling Branch, said the nature of the statements being made in the promotional pieces often dictates how long it can take FDA to give sponsors advisory feedback.

“The more direct your pieces are, the closer they are to your label, the more likely you’ll get a quick turnaround,” she said. “The further you get, the more consults we’ll need” and the more time it will take.

**TALK TO YOUR REVIEWER**

Given the agency’s challenges in meeting the 45-day goal, sponsors should build in some extra time when they submit launch materials, Abrams said.

In addition, sponsors should talk to the OPDP reviewer handling the submission about realistic timeframes and how best to facilitate an efficient review. These communications should start before the launch materials are even submitted.

“I think close communications is critical,” Abrams said. “You want to let the reviewer know that the launch is coming. They are familiar with the product already. They’ve worked very closely with the medical review division when the product is being reviewed for approval on the draft product labeling.”

“Many folks in your company are very familiar with a product as far as the development of promotional material,” Abrams said. “We don’t have that luxury.”

Sponsors should not only alert OPDP reviewers on when to expect a submission, but also what the submission is going to include and which materials are most important.

“We have core launch materials, but we want to know what’s important to you so we can work on those first, and get you comments on those first,” Abrams said.

Sponsors also should think about what an agency reviewer would need to conduct an efficient review.

“What we have seen sometimes is incomplete submissions,” Abrams said. “Claims come in with materials without references, or claims come in with references, but they aren’t annotated. It just makes for a more complicated review.”

“Many folks in your company are very familiar with a product as far as the development of promotional material,” Abrams continued. “We don’t have that luxury. So as easy and efficient as you can make the review for reviewer, hopefully you’ll get comments back.”

After submission, sponsors should check in with the OPDP reviewer on the status. “This does not mean calling them three times a week,” Abrams said, suggesting instead that sponsors ask the reviewer when they should check back for a status update.

“The bottom line is we know you want to launch these drugs,” Abrams said. “We want the materials to be truthful, balanced and non-misleading. We want good, credible information out there, so we’ll work closely with you to achieve that to get you timely comments.”

**A NEW LOW-WATER MARK FOR ENFORCEMENT LETTERS?**

Abrams also was asked the reason for OPDP’s low number of enforcement letters in the current calendar year. To date, OPDP has issued a total of four letters: one warning letter, and three untitled letters (see chart, p. 6). Two of the letters cited preapproval promotion of investigational drugs.
The low number of drug promotion enforcement letters in 2016 continues a downward trend seen since the agency issued 51 letters in 2010.

However, if the current number holds or even doubles by the end of the calendar year, 2016 could set a new low-water mark for drug promotion enforcement letters in recent history.

“I’m not sure that four is the lowest the agency has ever issued, but it certainly is within the last two decades,” said Wayne Pines, president of regulatory services and healthcare at APCO Worldwide.

Agency observers have attributed the enforcement letter decline, in part, to several recent and high-profile legal losses that the agency has sustained in First Amendment cases. The agency is conducting a comprehensive review of its regulations and policies on manufacturer communications about unapproved uses of approved products and will hold a public hearing on the issue Nov. 9-10.

“The topic of the decrease in the number of warning and untitled letters has been a topic of interest. We have received questions about this before,” Abrams said.

“Ultimately OPDP’s mission with our overall oversight program is to ensure that prescription drug promotion is truthful, balanced and non-misleading,” he said. “Issuing untitled and warning letters is just one component of a multifaceted program to achieve this objective.”

“We put many efforts to ensure compliance by industry, including our work on guidances, our work inviting comments on draft promotional materials and in doing outreach with our stakeholders. Our top priorities in OPDP are guidance development, review of draft product labeling, review of TV ads and core launch materials, enforcement,” training and communications, Abrams said.

OPDP will continue to devote additional resources to activities such as guidance development and review of draft promotional materials to increase voluntary compliance, he said.

Published online September 28, 2016

CDER Drug Promotion Enforcement Letters In 2016

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<tr>
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<th>COMPANY AND PRODUCT</th>
<th>LETTER TYPE</th>
<th>VIOLATION</th>
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<td>Hospira's <em>Precedex</em> (dexmedetomidine)</td>
<td>Untitled</td>
<td>Omission of risk information and material facts; failure to submit under Form FDA-2253</td>
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<tr>
<td>3/29/2016</td>
<td>Shionogi's <em>Ulesfa</em> (benzyl alcohol)</td>
<td>Warning</td>
<td>Omission of risk information and material facts; failure to submit under Form FDA-2253</td>
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<tr>
<td>8/25/2016</td>
<td>Celator Pharmaceuticals' <em>CPX-351</em></td>
<td>Untitled</td>
<td>Preapproval promotion</td>
</tr>
<tr>
<td>9/8/2016</td>
<td>Durect/Pain Therapeutics' <em>Remoxy</em></td>
<td>Untitled</td>
<td>Preapproval promotion</td>
</tr>
</tbody>
</table>

“Issuing untitled and warning letters is just one component of a multifaceted program” to ensure drug promotions are “truthful, balanced and non-misleading,” Abrams said.

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Big Pharma’s Big Debate Win

MICHAEL MCCAUGHAN pinkeditor@informa.com

The first Presidential debate could not have gone better for Big Pharma. There were no questions about, nor any stray comments on, the headlines about drug prices in the U.S. In fact, the wide-ranging topic list ended up excluding health care altogether.

Given the Hillary Clinton campaign’s embrace of drug pricing reforms, along with past statements by Donald Trump declaring his support for Medicare price negotiation, the lack of discussion of the topic during a broadcast viewed by tens of millions of Americans is a huge relief for biopharma companies.

Since there is a clear difference between the two campaigns on the future of the Affordable Care Act, health care will no doubt be a prominent topic in future debates. But the viewing audience will not match the numbers who tuned in for the first debate.

As an added bonus for US-based companies, the two candidates ended up agreeing that proposals to allow for repatriation of overseas income is a good idea.

That detail came out amid a typical period of cross-talk between the two candidates. Trump defended his tax plan as a job-creation bill, saying that companies are “going to bring $2.5 trillion back from overseas, where they can’t bring the money back, because politicians like Secretary Clinton won’t allow them to bring the money back, because the taxes are so onerous.”

Clinton responded by questioning whether Trump’s tax plan does not in fact include repatriation, but also that she supports it. “We’ve looked at your tax proposals. I don’t see changes in the corporate tax rates or the kinds of proposals you’re referring to that would cause the repatriation, bringing back of money that’s stranded overseas. I happen to support that.”

The debate also included the two candidates expressing violent agreement in opposing the Trans-Pacific Partnership trade agreement, with the “debate” focusing on the extent to which Clinton changed her view (and, by implication, her potential to switch back to supporting the deal after Election Day). Clinton’s defense – that she hoped it would be a good deal when the negotiations began but wasn’t happy with the final product – isn’t so different from the industry’s disappointment that the final agreement only includes a baseline five-year of data exclusivity for biologic medicines.

The biopharma industry can only hope that drug pricing stays in the background as the campaigns head into November.

Of course, they will still need to prepare for what happens after Inauguration Day.

From the editors of the RPM Report. Published online September 27, 2016

FDA’s ANDA Approvals

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<tr>
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<td>250 mg/2.5 mL (100 mg/mL); injection</td>
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<td>Apotex</td>
<td>Drospirenone/ethinyl estradiol</td>
<td>3 mg/0.03 mg; oral-28 tablet</td>
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<td>325 mg/50 mg/40 mg; tablet</td>
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<td>Aurobindo</td>
<td>Ayuna (ethinyl estradiol/levonorgestrel)</td>
<td>0.03 mg/0.15 mg; tablet</td>
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<td>Incassia (norethindrone)</td>
<td>0.035 mg; tablet</td>
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<td>Itraconazole</td>
<td>100 mg; capsule</td>
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<td>Aurobindo</td>
<td>Zoledronic acid</td>
<td>EQ 4 mg base/5 mL; injectable, IV infusion</td>
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Tentative Approvals

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<td>Olopatadine HCl</td>
<td>0.2%; solution</td>
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<td>Gland</td>
<td>Esmolol HCl</td>
<td>100 mg/10 mL; injection</td>
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<tr>
<td>Amneal</td>
<td>Memantine HCl</td>
<td>7 mg, 14 mg, 21 mg and 28 mg; extended-released capsule</td>
<td>9/28/2016</td>
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</table>
Reimbursement

As Drug Value Frameworks Gain Traction, Patients Seek More Input

CATHY KELLY Catherine.Kelly@informa.com

Patient groups could have a key role in shaping drug value assessment frameworks as the tools evolve and move toward solidifying a role in prescribing and coverage decisions, according to comments at an International Society for Pharmacoeconomics and Outcomes Research meeting on value frameworks Sept. 23.

Two key takeaways from the meeting were:

1. The frameworks are here to stay, despite continued opposition from drug firms to many of them, and
2. There is an opportunity for patients to influence how the frameworks are structured and used.

The meeting was held as part of a new ISPOR initiative to develop best practice recommendations on the appropriate definition and use of value frameworks for drugs.

Drug manufacturers are also expected to take advantage of the opportunity to participate in the ISPOR effort, which includes employees of the Pharmaceutical Research and Manufacturers of America on its steering committee. Manufacturers have opposed the new frameworks based on concerns they will influence prescribing or coverage decisions based on a narrow set of cost and effectiveness metrics that may not allow for different patient preferences, among other issues.

Health policy expert Mark McClellan welcomed the ISPOR initiative in the keynote address at the meeting. “This is the year of value frameworks isn’t it? There are a lot of them out there and it’s time to undertake an effort like this one to make sure we’re getting it right,” he said.

McClellan is director of the Robert J. Margolis Center for Health Policy at Duke University and was formerly FDA commissioner and administrator of the Centers for Medicare and Medicaid Services.

He noted the drug value frameworks so far offer only “incremental” resources to prescribers and payers. However, he added, “one of the emerging uses [for the frameworks] and reason I think this is really the year of value frameworks, is that we are moving into payment reforms that are explicitly, at least in name, about value.”

Nevertheless, he emphasized, “you can’t have value-based payment without a value framework underlying it … that a lot of different stakeholders, particularly patients, actually have confidence in.”

McClellan added “to the extent that these value frameworks are moving along and becoming more widely used, the ones that are gaining the most traction are the ones that don’t just talk about focusing on patients but actually have credibility for capturing what really matters to patients.”

As ISPOR and framework developers fine tune the tools, McClellan suggested “a good focus should begin with getting a model that stakeholders can broadly accept. Thinking carefully about matching a value framework with its intended purpose and audience is important for that.”

He advised “thinking carefully about what constitutes the elements of value. Is it just outcomes? Is it reduced anxiety? Is it other impacts of treatment such as productivity, maybe reduced infection rates? All of those could potentially go in.”

The value frameworks have grown out of the private sector in the US, which differs from Europe, where many such evaluation tools have come from the government. Most of the US developers are health care providers and a number of the frameworks so far focus on oncology drugs (see box).

In general, the value frameworks use comparative effectiveness analyses in a systematic way to assess the value of a drug relative to its cost. But the existing frameworks vary in their approach to evaluation and in their targeted end user.

Frameworks developed by the American Society for Clinical Oncology, the National Comprehensive Cancer Network and the American College of Cardiology with the American Heart...
Association are geared mainly toward assisting physicians and patients with prescribing decisions.

**QUANTIFICATION IS THE CHALLENGE**
A framework developed by the non-profit Institute for Clinical and Economic Review (ICER) is aimed at guiding reimbursement policies. The ICER evaluations encompass comparative effectiveness, cost-effectiveness and budget impact elements.

The framework sponsored by Memorial Sloan Kettering Cancer Center in collaboration with research and consulting firm RealEndpoints, is meant to inform patients and policymakers about the value of cancer drugs relative to their price. RealEndpoints’ RxScorecard also produces value scores for multiple drugs, both marketed and in development, across categories.

The framework developers offered ISPOR suggestions at the meeting regarding key issues that should be considered for frameworks. For example, ICER Chief Science Officer Dan Ollendorf pointed out “if there is an attempt … to come up with a quantified value framework that has multiple attributes but is still quantified only, you’re going to hear from the patient community and I don’t think it’s going to be pretty.”

“There are certain constructs that just can’t be quantified because they’re so disease-population specific that it would be difficult, if not impossible” to do so, Ollendorf said.

RealEndpoints CEO Roger Longman said that “any value framework that is going to be accepted and used has to reflect multiple points of view around value definition. If it can’t do that, it will not be used.” He explained that different points of view can be accommodated by “customizing the weights of each of the elements to reflect the relative importance within your decision-making. There is no one-size-fits-all analysis.”

**PATIENT-FOCUSED FRAMEWORK PLANNED BY FASTERCURES, AVALERE**
A new value framework for drugs, designed to primarily represent the patient perspective, is being planned by research advocacy organization FasterCures in partnership with Avalere Health.

The framework will address the value and cost of treatment to the individual patient, as well as the strength of evidence underlying an assessment of value. It will seek to support shared decision-making between prescribers and patients and to include a patient-friendly tool that is easily understandable.

The groups plan to present a draft version of the framework at the Faster Cures “Partnering for Cures” conference in mid-November.

The frameworks are all continuing to evolve and ISPOR will work to help direct their progress with development of a policy white paper. A draft version is scheduled to be released in early 2017.

**EXPANDING THE BREADTH OF COST-EFFECTIVENESS ANALYSIS**
The initiative was prompted by the determination that "each of the recent value frameworks has strengths and weaknesses but those vary and each has important limitations," according to a tentative work plan for the project.

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**DRUG VALUE FRAMEWORK SPONSORS IN THE US**

- American Society for Clinical Oncology
- National Comprehensive Cancer Network
- American College of Cardiology/American Heart Association
- Institute for Clinical and Economic Review
- Memorial Sloan Kettering Cancer Center/RealEndpoints
- FasterCures/Avalere

In addition, the group determined that “expanding the breadth of cost-effectiveness analysis has the potential to capture and reflect some … other elements of value that can be important for health sector decision-making.” ISPOR President Lou Garrison, professor emeritus of the University of Washington School of Pharmacy, told the meeting that the patient perspective will be an important contributor to those additional elements of value.

Garrison also noted that ISPOR will have to consider “trade-offs” between the various attributes of value that go into the framework.

National Health Council Senior VP Eleanor Perfetto agreed, pointing out that “patients are ready and willing to have conversations about those trade-offs. They’re just usually not included in the conversation. And if they’re included [in deliberations] early enough, you’ll find out there are some attributes you can take off the list and not even ask them to trade off because they don’t care about them.”

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October 3, 2016 | Pink Sheet | 9
Amgen’s Amjevita Approved As First Biosimilar To AbbVie’s Humira

SUE SUTTER sue.sutter@informa.com

With its fourth biosimilar approval, FDA has once again shown that its thinking about how to label such products continues to evolve.

In the case of Amgen Inc.’s Amjevita (adalimumab-atto), FDA took the opportunity to adjust its biosimilar labeling approach on indications for which the reference product sponsor still holds exclusivity.

Amjevita is also the first biosimilar approval for Amgen, which has eight other programs in its biosimilar pipeline.

FDA approved Amjevita, a biosimilar to AbbVie Inc.’s Humira (adalimumab), on Sept. 23, marking the fourth US biosimilar approval and the first one referencing the blockbuster tumor necrosis factor inhibitor.

Amjevita is also the first biosimilar approval for Amgen, which has eight other programs in its biosimilar pipeline.

“Approval of Amjevita is an exciting accomplishment as it marks a new chapter in Amgen’s story of being a leader in biotechnology,” Sean Harper, Amgen executive VP-R&D, said in a release. “In addition, Amjevita holds the potential to offer patients with chronic inflammatory diseases an additional treatment option.”

Approval followed a unanimous advisory committee recommendation in July. The panel concluded that the totality of the analytical, nonclinical, clinical pharmacology, comparative clinical efficacy and safety, and immunogenicity data support licensure as a biosimilar in arthritic, dermatologic and inflammatory bowel disease indications.

A DIFFERENT APPROACH ON ORPHAN CLAIMS

Amjevita is labeled for seven of the indications on Humira’s label but lacks four indications that are still protected by orphan drug exclusivity (see box).

Amgen did not seek approval of the orphan-protected claims. Nevertheless, the absence of any reference to them in Amjevita labeling is noteworthy because it marks a departure in FDA’s previous approach on orphan-protected claims under the 351(k) approval pathway.

FDA approved Celltrion Inc.’s Inflectra (infliximab-dyyb), a biosimilar to Janssen Biotech Inc.’s Remicade (infliximab), in April with labeling that suggested the biosimilar was safe and effective for the orphan-protected use of pediatric ulcerative colitis. Labeling stated that Inflectra had been demonstrated to be safe and effective “in another pediatric indication” but was not approved for this claim due to Remicade’s marketing exclusivity.

Celltrion had sought approval for the pediatric ulcerative colitis indication. At the FDA advisory committee review of the biosimilar, FDA said it would not be able to approve the claim until orphan protection expired but wanted panel discussion on whether there was sufficient scientific justification to extrapolate data to support a determination of biosimilarity for this use.

FDA’s decision to open the door to discussion of an orphan-protected claim was sharply criticized by the National Organization for Rare Disorders, and the agency’s approach to the orphan issue with Amjevita labeling suggests the agency may have had a change of heart.

In the Pediatric Use section of labeling, there is no reference to either studies, or a demonstration of efficacy or safety, in JIA patients between the ages of two and four years old or in pediatric Crohn’s disease patients. There also is no mention in Amjevita labeling of trials, efficacy or safety for treatment of hidradenitis suppurativa or uveitis.

Studies of the orphan-protected indications that are included in the Warnings and Precautions, and Adverse Reactions, sections of Humira labeling are not referenced in Amjevita labeling.

BIOSIMILARITY STATEMENT UNIFORMITY

However, FDA has seemed to have settled on a uniform approach to explaining biosimilarity in labeling.

The Highlights section describes Amjevita as a biosimilar to Humira, with a footnote explaining what this means and that biosimilarity has been demonstrated for the indications, dosing regimens,
While Amjevita’s labeling largely tracks that of Humira, there are some differences resulting not only from the absence of the orphan-protected claims but also differences in product presentation.

Humira is available in seven single-use presentations: two prefilled pens, four prefilled glass syringes and one glass vial for institutional use. In contrast, Amjevita is approved in only three single-use presentations: one prefilled SureClick autoinjector, and two glass syringes.

A PIECE OF AMGEN IN THE BRAND NAME
Amjevita becomes the third biosimilar with a random, four-letter suffix in its proprietary name.

The first biosimilar, Sandoz’s Zarxio (filgrastim-sndz), is the only one with a suffix directly derived from the company’s name, although Erelzi’s “szzs” suffix walks the line between meaningful and nonmeaningful.

Industry has opposed FDA’s proposal, laid out in an August 2015 draft guidance, that distinguishing suffixes should be devoid of meaning. Industry groups, companies and other stakeholders overwhelmingly have said they prefer memorable suffixes derived from a sponsor’s name.

However, Amgen still appears to have found a way to get some derivation of its company name in the biosimilar name, with the brand’s first four letters, “Amje,” closely resembling those of the sponsor.

LAUNCH TIMING UNCLEAR
As has become standard for any new biosimilar, it remains unclear when Amjevita might actually get to market.

Amgen and AbbVie have been engaged in the so-called “patent dance” under the Biologics Price Competition and Innovation Act. AbbVie filed a patent infringement suit against Amgen Aug. 4, claiming Amgen’s biosimilar infringes 61 of the more than 100 patents that cover Humira. Amgen opted to limit the number to be litigated in the first wave of litigation and thus only 10 are cited in the complaint. AbbVie also claimed Amgen did not provide any information beyond its BLA describing the processes to manufacture its biosimilar.

In a Sept. 13 response to the complaint, Amgen said it fully complied with its obligations under the BPCI Act and that its BLA contains extensive information concerning the biosimilar (also known as ABP 501), including information that describes the processes used to manufacture the product. Amgen also made counterclaims, saying that AbbVie did not provide adequate responses in the patent information exchange process.

Amgen also stated that it would provide 180-day notice of its intent to launch ABP 501 after FDA licensure.

A scheduling conference is set to be held in the US District Court for the District of Delaware on Oct. 27.

In a statement, AbbVie said: “We anticipated Amgen’s product would be approved. AbbVie and Amgen are currently in litigation over AbbVie’s Humira-related intellectual property.” The company declined to discuss specifics on the litigation.

AbbVie has waged a fierce battle to protect Humira from biosimilar competition. In addition to various citizen petitions, it met privately with FDA officials several days before the Amjevita advisory committee meeting to make the case against approving the biosimilar for inflammatory bowel disease.

Brenda Sandburg contributed to this report. Published online September 23, 2016
Biosimilars offer a “tremendous” opportunity for improving access to biological medicines and keeping national healthcare costs down, but the market will only be sustainable if manufacturers and payers can reach a common understanding of the benefits of biosimilars in both the short and long term, says a new report.

While the two parties agree on some issues regarding the biosimilar market, there is something of a gulf between them on others, according to the report by consultancy Simon-Kucher & Partners. For example, while industry wants to see multiple companies participating in order to keep up the market share of biosimilars, payers are not really concerned about the number of companies involved and are happy as long as they can have cheapest drug with the highest market share.

Similarly, companies want a “fair” starting price for biosimilars followed by gradual price erosion, while payers tend to push for immediate sharp discounts. Positions are also entrenched when it comes to the role of payer guidance: many companies feel the payers should actively use guidance to drive biosimilar usage, but payers on the whole feel that their guidance is already up to the job, says the report, which was produced for the Biosimilar Medicines Group, part of the European generics and biosimilars industry association, Medicines for Europe.

The report proposes 13 “principles for a sustainable biosimilar market,” which draw a number of conclusions. To summarize, it concludes that biologics (including biosimilars) are complex molecules that require a tailored pricing and market access policy (P&MA), and while they are “very valuable” for the healthcare systems by generating savings and improving patient access, their benefits will only be reaped if there is healthy competition among manufacturers. This in turn will depend on the existence of “a sustained market attractiveness from a manufacturer and payer perspective.” Moreover, biosimilar medicine policies will require appropriate monitoring and maintenance over time.

Carol Lynch, chair of the BMG and global head of biopharmaceuticals at Sandoz, said the report showed that a sustainable biosimilar medicines market was one that provided continued benefits to all stakeholders: increased access for patients, more treatment options for physicians, sustainability healthcare budgets for payers, and business opportunities for manufacturers.

“Beyond the payer-industry relationship, a multi-stakeholder approach is crucial to develop a sustainable biosimilar medicines market and gainingshare in particular has proven to be a successful driver for increased utilization of biosimilar medicines in medical practice throughout Europe providing benefits to all stakeholders,” Lynch stated.

In researching the report, the authors set out to assess the impact of national policies on market uptake and price of selected biosimilar medicines such as filgrastim and epoetins, based on research into expectations and current practices in the biosimilars market in seven EU/EEA countries: France, Germany, Italy, Norway, Poland, Spain and the UK.

The report examines current pricing and market access policies in these countries, the impact of those policies on national uptake and price, the estimated savings through use of biosimilars, different purchasing practices, the effect of discounts on savings and access, and the effects of biosimilar use on access and treatment guidelines.

Among other things they found that manufacturers felt that biosimilar sustainability required a predictable market over the longer term, involving multiple biosimilar players and a price-volume combination that allowed continuous investment. Payers, by contrast, were more concerned with creating quick financial savings without jeopardizing current treatment standards.
NINE CRITERIA
Their report identifies nine criteria for the “ideal sustainable biosimilars market”:

- A high biosimilar market share.
- A “fair” price level for biosimilars.
- Commercial attractiveness.
- An acknowledgment during the pricing and market access process of the high degree of complexity of biologics.
- Maintaining healthy competition.
- Payer guidance on the use of biosimilars versus the originator drug.
- A low effort needed to monitor and enforce payer policies.
- Parallel sourcing from multiple manufacturers.
- Earlier and broader use of biosimilars in additional patient segments.

Presenting the report on Sept. 23, Michael Dilger, a partner with Simon-Kucher & Partners, said that the list “may not be comprehensive, but from our discussions these nine came out as the most important for sustainability.” He outlined the attitudes of manufacturers and payers to some of these criteria, and at the differences between those attitudes.

For both parties, a high biosimilar market share was an important factor, although views differed as to the number of companies taking that share. One payer is quoted as saying that the most important factor is “the highest share for the least expensive alternative and this is mostly a biosimilar.” Less relevant for the payer was where the product came from – ie, it didn’t matter who the manufacturer was.

Industry by contrast felt that if the biosimilar share was high, multiple manufacturers would be able to take part in the market. For manufacturers, policies that maximize the market share of the least expensive drug “may reduce competition in the long term, which also cannot be in the interest of payers of course as it would also decrease their negotiating power and limit the savings potential.”

PAYER GUIDANCE
Payer guidance was something that manufacturers felt should play a key role in encouraging biosimilar uptake, saying payers were responsible for using their guidance to drive uptake “more intensively”. One manufacturer told the consultants that payer guidance was “crucial” although payers also needed to do something to “increase the acceptance of biosimilars among physicians.” There was some “implicit criticism” from industry that payers could do more, and that their guidance was not always implemented strictly, Dilger commented.

By contrast, only a few payers saw the need to improve their existing biosimilar guidance, most being of the opinion that it already drove biosimilar uptake adequately and that “if the market works well there is no strong need to put further payer guidance in place.” One said their country’s health ministry “guides physicians to use the least expensive treatment alternative, which is usually a biosimilar. I believe this measure is key and already secures sufficient biosimilar uptake.”

So they “agree on the importance of guidance, but differ on the extent of guidance needed and on what has already been done,” Dilger observed.

A FAIR PRICE TO PAY
While manufacturers and payers find common ground in desiring a “fair” price for a biosimilar, there is less agreement over what “fair” means. The industry view overall was that payers in several markets had P&M policies in place that “implicitly” required companies to “immediately offer a high discount in order to stay in the market” (e.g., single winner tenders) whereas companies would prefer moderate discounts to begin with.

Payers, though, countered that they do not always ask companies for high discounts and often industry itself offers voluntary price concessions of 50% or more. One said they saw a discount of 40-50% as sustainable in general, but that this should be nearer to 50-70% “when talking about very successful drugs such as Enbrel, Humira etc.”

While companies stress the complexity of biosimilar medicines development, production and supply, and say this is a crucial argument to be taken into account in market access policies, payers say this complexity is already considered in those policies. So there was some disagreement over how important this criterion was in terms of market sustainability.

As for competition over the long term, payers agreed that competitive behavior was important to achieve bargaining power in price negotiations, but disagreed on the need for multiple biosimilar manufacturers in the marketplace for one active substance, saying it was enough if the tender winner served the market – ie, one manufacturer takes all.

“Generating savings is by nature a short term thing, payers have annual budgets, and therefore “they don’t look five or ten years into the future where the effect of policies that limit competition may be more obvious”, the report says. If manufacturers see competition is limited, “they may take decisions not to invest in certain development or not to launch later on in certain markets.”

GAINSHARING AGREEMENTS
The report also mentions the role of “gainsharing”, saying it has proven to be a “successful driver of biosimilar uptake across multiple markets” with benefits for all stakeholders. This includes initiatives such as non-cash gainsharing at the hospital level (e.g., savings allow more patients to be treated within the same budget), direct gainsharing in hospitals through, for example, allowing them to re-allocate savings to health units, and gainsharing at physician level where doctors may split the savings with the health insurance.

Gainsharing is most effective if the healthcare provider sees tangible benefits from generated savings (additional services for patients, improved working conditions, monetary benefits, etc), it adds.

From the editors of Scrip Regulatory Affairs. Published online September 27, 2016
Lilly’s Sarcoma Drug Lartruvo Latest To Test EU Conditional Approval System

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The latest drug to receive a recommendation for conditional marketing authorization (CMA) from the European Medicines Agency is a new treatment for soft tissue sarcoma, Lilly’s Lartruvo (olaratumab), which when used with doxorubicin has been shown to improve survival compared with the older drug alone.

Eli Lilly & Co. said that the opinion from the EMA’s scientific committee, the CHMP, was “the first regulatory step in the world towards approval for olaratumab,” and that this was also the company’s first ever conditional approval recommendation in the EU.

The CHMP recommendation – it will be marketed for adults with advanced soft tissue sarcoma that has not responded to treatment with radiotherapy or surgery and who have not previously taken doxorubicin.

Lartruvo is a human IgG1 MAb and an antagonist of platelet-derived growth factor receptor-alfa expressed on tumor and stromal cells, which according to Lilly means it may cause anticancer activity by targeting tumor cells directly as well as the cells that surround and support tumor growth.

The EMA will be watching carefully to see whether Lilly produces the data it has agreed to provide in return for getting the conditional approval opinion, not least because the CMA mechanism is itself under close scrutiny in light of suggestions that it is not working as intended.

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The EU submission was based on data from JGDG, a Phase II, open-label randomized trial comparing olaratumab, in combination with doxorubicin, with doxorubicin alone. Efficacy endpoints included progression-free survival, overall survival, and objective response rate.

Lartruvo is clearly of great scientific interest to the EMA: as well as gaining an early recommendation through the conditional approval mechanism, the drug was granted orphan status in February 2015, and was reviewed by the CHMP under the accelerated assessment mechanism, which is used for drugs considered to be of major public health interest, particularly from the point of view of therapeutic innovation.

Assuming the drug is granted a CMA by the European Commission – which would be expected two to three months after the CHMP recommendation – it will be marketed for adults with advanced soft tissue sarcoma that has not responded to treatment with radiotherapy or surgery and who have not previously taken doxorubicin.

APPROVAL CONDITIONS

As a condition of the CHMP approval recommendation, Lilly will need to provide results from the ongoing Phase III ANNOUNCE study, whose estimated study completion date, according to clinicaltrials.gov, is February 2019.

Until the full data from the trial are available, the CHMP will review the product’s benefits and risks on an annual basis in order to determine whether the CMA can be maintained, Lilly said. Once the obligations in the CMA have been met, it can be converted into a full marketing authorization. This aspect of the product’s dossier will no doubt be closely monitored to ensure the company honors its obligations.

The conditional approval system came under the spotlight earlier this year when an official from the commission said it was important to ensure that companies actually fulfilled the “specific obligations” they agreed to at the time of the CMA.

Speaking at Informa’s EU Pharma Law Forum in Brussels in May, Florian Schmidt of the pharmaceutical unit in the commission’s health directorate also noted that while a conditional approval can be withdrawn if the company fails to meet its obligations, this has never happened in practice. He said that about half of the products with a CMA had had the deadlines for meeting the obligations changed because the companies said they were not able to meet them in the agreed timeframe.

Concern about the CMA had earlier been expressed by the commission’s Pharmaceutical Committee, which in 2014 raised issues such as failure to fulfil post-authorization commitments in a timely manner so that the data “lose their value for regulatory purposes,” and a shortage of clinical and cost effectiveness data from real-life settings.

Similar concerns were flagged by the Council of the EU in its “Conclusions on strengthening the balance in the pharmaceutical systems in the EU and its member states,” published in June this year. Among other things the council said there were “indications that the post-market compliance with certain obligations for marketing authorization holders is not always optimal,” which might mean that “independent research data and information from patient registries are often not structurally generated, collected and made available for research and proof of effectiveness and safety.”

RESULTS SUBMITTED TO US FDA

The results of the Phase II study of olaratumab have also been submitted to the US Food and Drug Administration, which appears similarly impressed with the drug and granted it priority review status in May this year, having already awarded it a number of other designations, including breakthrough therapy, fast track and orphan drug.

Breakthrough therapy designation is designed to accelerate the development of a new drug intended for a serious condition where preliminary clinical evidence indicates that it may show substantial improvement over available therapies on a clinically significant endpoint.

From the editors of Scrip Regulatory Affairs. Published online September 26, 2016
Dublin The Odds: Ireland Plays On Strengths As It Prepares EMA Bid

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“The Irish government is preparing a formal bid to have the European Medicines Agency move to Dublin once the UK leaves the EU, according to health minister Simon Harris, who describes the EMA as a “prestigious” agency and the chance to host it as “one of the more interesting opportunities afforded by Brexit.”

Speaking at the BioPharma Ambition conference in the capital on Sept. 22, Harris said it was important that any disruption to the EMA’s work “should be kept to a minimum when it relocates from London, probably within the next couple of years,” and suggested that moving the agency to Dublin could be the answer, not least because the Irish Health Products Regulatory Agency (HPRA) is already closely involved in the work of the EMA.

The Irish Department of Health told the Pink Sheet that it was working on the bid with other government departments and state agencies, including the HPRA, and that the intention was to have the bid finalized “by the time Article 50 is triggered, which is expected to happen early in 2017.” The triggering of Article 50 will mark the beginning of a two-year period during which the UK and the EU will work on negotiating the terms of the UK’s exit.

Ireland is just one of several EU countries vying to have the EMA after its departure from the UK, which is seen as all but inevitable as a result of the EU referendum result. Among the candidates are Austria, Denmark, France, Italy, Poland, Spain and Sweden — the last of which has just laid out its case, describing the EMA as a “gem” in the life science environment.

At the Dublin conference, Harris, who has only been health minister since May this year, explained why he thought Ireland would be the best choice. He said it had an “excellent track record in regulating medicines and medical devices,” and that this was “due in no small part to the work of the HPRA, which enjoys an international reputation.”

Describing the HPRA as “proactive and committed,” he said it played an important role in the EMA’s activities, and that its staff were involved in a number of the agency’s committees and working parties, including the position of vice-chair of the Pharmacovigilance Risk Assessment Committee and the chair of the Committee for Medicinal Products for Veterinary Use.

He also noted that “nine out of the ten largest pharmaceutical companies” now had operations in the country, and that “collaborative clusters in pharmaceutical, biotechnology, medical devices and diagnostics” had been a key factor in the growth of the sector in recent decades.

“I know that your industry will support our efforts to bring this prestigious agency to Dublin,” he told delegates at the conference, which was organized by the Irish Pharmaceutical Healthcare Association (IPHA), BioPharmaChem Ireland, and the National Institute for BioProcessing Research and Training. IPHA’s president, Leisha Daly, said last month that Ireland was “ideally placed as a hub of pharmaceutical innovation and research to be the new location for the EMA,” according to the Irish Medical Times.

The DoH said it believed that a move to the Irish capital would allow the EMA’s current standards of excellence to be maintained, thus “ensuring continued protection of EU citizens and providing reassurance to the industries which it regulates.” The agency would benefit from proximity to the HPRA, which would “provide strong support in the event of a move,” it said.

Dublin has an airport some 20-30 minutes from the city center, it added, with “excellent air connectivity with EU capitals and internationally and continuing expansion of routes served.”

The department also flagged up the linguistic and cultural comforts Ireland had to offer, saying it was “an English language location” and that English was “the working language of the EMA and the pharmaceutical industry.”

Regarding the inevitable worries among EMA staff over the likely relocation, the DoH offered some reassurance, saying that in terms of retention of expertise “we believe that Dublin’s proximity to London will prove attractive to some existing EMA staff. Staff with families well established in the UK capital might decide to commute, while commonality of language and other facets of life may make it more likely that staff would remain with the EMA rather than leave, when it has to move from the UK.”

ACCESS TO RESEARCH FUNDING

As well as the implied loss to the UK when the EMA moves from London, the health minister touched on another rather sensitive Brexit-related issue, access to EU research programs and funding — something that will have many in the UK life sciences area gnashing their teeth anew over the implications of the referendum result.

He said that Irish health researchers “are successfully competing at the highest level for EU funding, as evidenced by their success in securing over €30m ($33.5m) in funding from Europe’s flagship research programme, Horizon 2020.”

Concerns have already been expressed by some UK universities over their exclusion from some Horizon 2020 projects as well as the issue of freedom of movement of researchers in a post-Brexit Europe.

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Novartis Tests Global Manufacturing Process For CAR-T Therapy

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ATLANTA - A multi-center Phase II clinical trial Novartis AG is sponsoring will show whether the Swiss drug maker can scale up a personalized leukemia treatment for global manufacturing.

A commercial-scale clinical trial may be unusual, but so are many aspects of manufacturing a chimeric antigen receptor T cell therapy like the one the University of Pennsylvania has been developing, CTL019, and that Novartis hopes to commercialize.

Novartis was an early leader in the CAR-T space, although the recent announcement that it is shuttering its cell and gene therapy unit raised some doubts about its long-term position. Nonetheless, the study could provide some significant insights about commercial manufacturing of a cell therapy and Novartis said it still aims to file CTL019 at FDA in early 2017 for relapsed/refractory pediatric acute lymphoblastic leukemia. Kite Pharma Inc. says it is on track to file its CAR-T candidate, known as KTE-C19, in late 2016, with Juno Therapeutics Inc.'s JCAR015 somewhat behind the leaders.

UPenn had been manufacturing CTL019 for initial trials at several academic GMP cell manufacturing facilities. While results were encouraging, the manufacturing processes it had been using were too manual for commercial-scale operations.

“There’s no way that the University of Pennsylvania is going to be making cells for a global manufacturing process,” Stephan Grupp, a pediatrics professor with the university and pediatric oncologist with the affiliated Children’s Hospital of Philadelphia, said Sept. 18 at the International Society for Pharmaceutical Engineering annual meeting in Atlanta.

“Not only are we not suited, we’re not capable and we don’t want to do that,” explained Grupp. “We want to innovate and pass things on to pharma. That’s always been what’s worked in the past, and it’s what ought to work in the future.”

The treatment that UPenn researchers devised attacks cancer of one part of a patient’s immune system by bioengineering another. They use lentiviral vectors to enable one type of lymphocyte, T cells, to target another type, B cells, as a way of treating B cell cancers like ALL. Consensus has grown that CTL019 and the competing candidates will require a very different approach to manufacturing.

“The field is changing underneath our feet even as we are trying to implement these processes.”

– UPenn’s Stephan Grupp

AERIAL VIEW OF THE BASEL CAMPUS, NOVARTIS HQ.

“Processes Changing on the Fly

“If you think about it from a bone marrow transplant perspective, everybody’s got a stem cell lab, everybody collects their own cells, everybody processes their own cells, and then they give them back to the patient,” Grupp told the ISPE meeting. “Now everybody imagined that cell therapy might be the same thing, but that hasn’t worked.”

One challenge with the small-scale stem cell laboratory approach is establishing comparability, he said. It is difficult to convince regulatory authorities that different labs can make the same product, particularly given that it’s difficult to say which of the complex cell-based biological therapy’s attributes are critical to performance.

“It was immediately clear to Novartis, and the other two cell therapy companies, Kite and Juno, followed suit, that this was going to have to be a centralized process where we collect cells, we send them to a cell manufacturing facility, they make the cells and they send them back. … So centralized cell manufacturing seems to be the way the field is going.”

While there is FDA guidance, it’s still in draft form, which points to another problem, he said: “Right now, there isn’t a defined set of SOPs that everybody agrees is the only way to make cells.”

Cell manufacturing processes remain in flux, he said. “The field is changing underneath our feet even as we are trying to implement these processes.”

To go from academic to commercial-scale GMP, Novartis and the university went through a pre-transfer process “where we tried to characterize what we were doing in the lab as well as possible then transfer to centralized cell manufacturing.”

He said the process of establishing commercial-scale standard operating procedures, achieving reproducibility and treating patients “has been harrowing and also incredibly exciting.”
It's been particularly challenging for the commercial-scale chemistry, manufacturing and controls team, he said: "Their heads are exploding over this. ... They're like, 'are you kidding me? Are you actually going to change the process on the fly?'"

**SOME KEY MANUFACTURING CHALLENGES**

Grupp shared some of the key challenges with commercializing a cell therapy like CTL019.

Because there is one lot of one product for each patient, release testing can be expensive and challenging.

And the unusual nature of the product poses additional challenges for certain standard quality control release tests. For example, it is difficult to come up with a potency test that makes sense. The bioengineered T cells quickly proliferate in patients, typically by 10,000- or 100,000-fold in the first month, wiping out targeted B cells regardless of how few were injected or how many were needed. As long as the cells proliferate in a patient, they’re potent.

Another issue is that commercial-scale manufacturing will require automation, and "automation is nowhere close to this process yet," Grupp said.

In addition, the supply chain issues are significant. For the multicenter trial, patients’ T cells are collected from as far away as Australia, frozen and sent to the Novartis facility in Morris Plains, NJ, where they are re-engineered into cancer killers, refrozen and shipped back. Novartis must be sure whose cells they are throughout the process to avoid treating another patient with them.

**A TECH OPS VIEW OF THE CHALLENGES**

Speaking at the Parenteral Drug Association’s annual meeting in Las Vegas last year, Jeff Boyd, head of technical operations for the now-disbanding Cell and Gene Therapies Unit at Novartis’ Morris Plains site, provided another perspective on how the company has approached the GMP and cost-of-goods challenges associated with manufacturing the autologous cell therapy.

Boyd said UPenn researchers chose to partner with Novartis for commercialization because of the way the company had brought tyrosine-kinase inhibitor Gleevec (imatinib) to market so quickly.

The researchers were particularly interested in partnering with an organization that could support the transition to a large cGMP manufacturing facility and that could develop a sophisticated tracking system to ensure overall chain of custody, said Boyd.

Novartis and the university signed a collaboration and license agreement in August 2012. That December, Novartis bought the Morris Plains, NJ, facility where Dendreon had manufactured its lead product, Provenge (sipuleucel-T) — a pioneering, but commercially unsuccessful autologous cell therapy that targets prostate cancer.

Boyd emphasized the role of value-stream mapping and spaghetti diagramming in improving the manufacturing process, as well as the importance of optimizing the whole system rather than each of its components.

He also touched on the difficulty of process characterization, what it means to characterize T cell percentages or to determine transduction efficiency for example, and on the challenge of developing a potency assay for release testing.

Boyd also emphasized the importance of variability reduction, always a priority in assuring and controlling quality, but especially important in cell therapy due to the high variability among the cells themselves.

**STEP-WISE APPROACH TO FULL AUTOMATION**

He also spoke to the cost-of-goods challenge with the highly manual cell therapy manufacturing process, which needs to get less expensive for the therapy to become affordable enough to proliferate globally.

Rather than scale out by bringing more people, more human error and more variability into the manufacturing process, Boyd said Novartis chose to focus on automation.

"We need to take a stepwise approach progressing from a manual process to a semi-automated solution and ultimately to a fully automated solution," he said.

The process requires a lean quality control laboratory with rapid assays in place for quick test results, he said.

Boyd also argued that it’s important to advance from batch-and-queue processes of traditional clean rooms to continuous flow processes for autologous cellular therapies where there would be work cells with specialists assigned to each task.

The challenge, he concluded, is to bring down the manufacturing cost with automation, robotics and variability reduction.

"Our goal is to absolutely make this accessible to patients around the world."

The multicenter trial that’s now under way is where all these objectives dovetail. "It’s the real proof of concept as far as I’m concerned," Grupp told the ISPE meeting. "If we can’t make this work for our patients in a pharmaceutical setting, we’re not going to be able to deliver it across the world."

*From the editors of the Gold Sheet. Published online September 23, 2016*
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Investigation Failures, Root Cause Problems Continue To Bedevil Manufacturers

Investigations of manufacturing failures and detection of their root causes might be improved by a more systematic but open-ended approach to reviews or evaluation through a lens of best practices, experts suggested Sept. 13 at the Parenteral Drug Association/FDA joint regulatory conference in Washington.

They suggested that new more holistic approaches are needed given that health inspectors worldwide continue to see problems with inadequate investigations of why manufacturing lots fail to meet specifications and the inability of the pharmaceutical industry to detect the root cause of quality defects found in manufacturing operations – and there has been little progress in more than two decades.

As David Jaworski, a senior policy advisor in the FDA drug center's Office of Manufacturing and Product Quality, noted, despite the industry's adoption of International Council on Harmonization's Q10 quality systems guideline in 2010 and quality guru Joseph Juran's strategies to achieve optimal world class quality in the early 1990s, the industry has not made much progress over the past 25 years in achieving this vision.

He said that "pharmaceutical quality systems still lag in effectiveness for many of our companies; there are still too many recalls and adverse events that are traced to quality issues."

THE RIGHT AND WRONG WAY

Karen D'Orazio, a consumer safety officer for FDA's Center for Drug Evaluation and Research, shared two case studies showing the right – and wrong – way of conducting failure investigations.

These case studies were based on a review of 26 warning letters, untitled letters and regulatory meetings over three years, from July 2013 to July 2016. She found that failure to adequately extend investigations was found 13 times under 21 CFR 211.192, while failure to identify root cause was found six times. Not extending the investigation to other products was found four times and corrective action not adequate found three times.

One successful failure investigation involved a finished sterile powder fill operation for which FDA's district received field alert reports for complaints of cracked bottles.

The firm's practices called for inspecting glass bottles for stoppers and labels and placing those rejected for missing labels in a bin – and cracks occurred when the bottles hit the bin. In reviewing the cracks, the firm hypothesized that shipping was responsible for the cracks.

But it subsequently identified the correct cause by bringing in a material science expert, who examined the bottles and observed that tossing the bottles in the bin caused the cracks.

In contrast, D'Orazio cited an over-the-counter acne control product manufacturer that hypothesized on several causes of a...
failures, but neglected to then prove those were the right causes or to look beyond isolated incidents.

This firm rejected a batch for failing established microbial specifications. It concluded that the failure of the initial lot was due to the insufficient cleaning of a transfer pump, but had no data to support this conclusion. The pump was sanitized but the first lot afterwards also failed the established microbial specifications.

The firm then concluded that the source of the contamination was in the filling process, but was unable to specify why or where in the process that contamination occurred. It also didn't extend its investigation to other products.

D’Orazio said that “what they did was they said it was somewhere in the filling process. Then it was everywhere. They did not extend the investigation to other products.”

She commented that “this firm really did not have any good quality system to speak of. The water had been leaking and there were multiple excursions from microbial contamination from the water as well. The lab methods were not validated and the clearing method was not validated. The persons there did not understand their processes even well enough to understand the root cause.”

INFORMATION FIRST, NOT HYPOTHESES

Acknowledging the difficulties of conducting failure investigations, D’Orazio described her own experience outside of pharma to show how investigator bias can cloud the effort.

In her first job as an environmental inspector, her duties were to ensure appropriate air quality. She received complaints of poor air quality from the lower floors of an urban medical center. She was convinced the problem stemmed from vents circulating air that were located near a loading dock and a bus stop.

“I could not get out of my head that it had to be the same two intakes.” She told her supervisor that the problems could be fixed for $115,000. The supervisor told her to get another opinion.

They consulted an air quality control expert who disagreed with D’Orazio’s assessment, and said “let’s go across the street and see what’s going on.” The odors actually emanated from an incinerator across the street, which D’Orazio said was not supposed to operate during daytime hours. “Yet the smoke was always coming out. That picture was worth a thousand words … I was presuming I knew what the root cause was even before I did the inspection.” D’Orazio realized she was caught up in proving a theory and fitting the facts to that theory.

D’Orazio drew some lessons from the experience: don’t assume to know the root cause before beginning the investigation; bring in appropriate expertise early on to identify all the potential processes contributing to the problem and interview the right people.

Mark Paradies, the president of System Improvements in Knoxville, TN, echoed D’Orazio’s advice to develop as much information as possible before hypothesizing on the source of failures.

He focused specifically on effective root cause analysis and incident investigation. Among the “secrets” of effective reviews, he said, is understanding that “your root cause is only as good as the information you collect.” His comments suggested investigators should try to ask more questions on more varied issues, because often they ask the wrong questions.

For example, he showed a video of a driver nodding off before finally going to sleep. The accident report on the driver’s subsequent car crash never mentioned that he fell asleep. Investigators incorrectly attributed the accident to distracted driving, never asking if the driver was fatigued.

Paradies’ comments suggest the importance as well of wording questions in such a way as they are more likely to elicit needed information. People “never admit that they fall asleep, they say that ‘a dog ran out in front of me’ or ‘I don’t know what happened and the car rolled over,’ because they really don’t know what happened.” He noted that “one of the things I seldom see in industrial incident investigations is whether someone asks ‘are you fatigued?’”

Paradies, an electrical engineer, spent 31 years doing root cause work, and is the author of eight books on root cause analysis. He described the second “secret” as understanding what happened before probing why it happened.

He outlined a seven-step process to follow:

1. Plan the investigation.
2. Determine the sequence of events.
3. Define causal factors.
4. Analyze each causal factor’s root cause.
5. Analyze each root cause’s generic cause.
6. Develop and evaluate corrective actions.
7. Report and implement corrective actions.

“It was not just one guy’s fault. It is not that Joe screwed up. It is a whole bunch of things that led to this accident. We need to fix this and come up with a root cause for all of them. Figuring out what happened before why it happened gets you beyond assigning blame. You usually have multiple factors that have to be looked into.”

DON’T PLAY FAVORITES

Reinforcing D’Orazio’s concerns about the bias introduced by starting with a hypothesized cause, Paradies said the third “secret” is to understand that the investigator’s knowledge, or the lack of it, can get in the way of a good root cause analysis.

Paradies said that “I am going to say this is obvious but maybe it is not. Karen’s example is a good one. Her first investigation where she knew what the answer was, so that her knowledge got in the way of an investigation. … If you don’t know the cause of the effect...”
you observed, you probably will not find that cause because you will not have any knowledge of it. Should you be looking for things that you don’t know you should be looking for? That means your root cause effect is limited to your current knowledge.

Paradies said that some of the tools that the pharmaceutical industry uses to conduct a root cause analyses – the fishbone diagrams, the five whys and fault trees – depend on this cause and effect relationship, which is dependent on investigator knowledge.

This model assumes a level of expertise and also training that may not always be there. For example, many seasoned investigators lack training in human factors.

During his employment at DuPont, Paradies observed “very few” of the experienced system engineers who conducted failure investigations had training in human factors. “Guess what causes most accidents and quality problem? Someone screws up. Someone makes a mistake. That is what we get and we get problems and we get mistakes, so if we don’t have training on what causes those mistakes, how likely is it that we will understand the cause and effect relationship that result in these errors if you have never had training in this?”

Traditional approaches often assume expertise and training that might not be there. For example, many seasoned investigators lack training in human factors.

Investigators also should be wary of having a “favorite cause” for most problems, leading them to continue to search for that to be a cause until they find it, meanwhile ignoring many other questions that should be asked.

Paradies said that he developed a new definition of root cause to shift the emphasis from cause and effect, which is dependent on investigator knowledge, to a more systemic and holistic approach.

- The old root cause definition he used in 1986: “The most basic cause (or causes) that can be reasonably identified that management has control to fix.”
- The new root cause definition he started using in 2006: The “absence of a best practice or the failure to apply knowledge that would have prevented the problem.”

The new definition “allows manufacturers to focus on the lack of best practices in evaluating the problem. So what is the missing best practice and where is the knowledge that we should be applying to prevent these problems?”

**GOING BEYOND ROOT CAUSE**

Paradies suggested that the nuclear industry uses a more robust root cause analysis method that is worth considering in pharmaceutical manufacturing. Its model examines the generic cause of an accident and uses two tools: the “extent of the condition” and the “extent of the cause.”

The “extent of condition” evaluations are done soon after an accident to decide if additional immediate actions are needed to address the risk of additional failures while a root cause analysis is being conducted. Usually extent of condition looks for similar equipment related conditions. For example if a bearing fails are similar bearings used in similar circumstances or equipment that could also fail?

It can also be applied to human factors. For example if a valve is opened accidentally, are there similar valves that may be opened accidentally?

The “extent of cause” is usually performed after the specific root causes are identified that led to an accident. The extent of cause is used to decide if a specific root cause needs to be analyzed to find the generic cause behind the specific root cause.

Using this approach in drug manufacturing, he continued, “if you have product contamination, you would say ‘is this the only product that we have that gets contaminated or can there be other products that are contaminated and if they are contaminated is this cause in other places?’ So you are looking for the extent of the cause and the extended conditions.” If “you have the same cause in other places your corrective actions have to be more than just fix it here.”

**MAJOR GLOBAL PROBLEM**

The PDA/FDA conference presentations documented the extent of the failure investigations challenges as well as looking for new approaches to better investigations.

For example, Merck’s Anil Sawant said that the lack of adequate failure investigations was the top deficiency found in GMP inspections of Merck facilities worldwide.

A report prepared internally for Merck from inspectional observations said that inadequate “deviation management” was found in 37 inspections. The problems included failures to investigate discrepancies, inadequate investigations and ineffective corrective and preventive actions.

This was followed by inadequate documentation found in 18 inspections and then inadequate environmental control found in 16 inspections. Merck’s data was completed from inspectional data from FDA, the European Medicines Agency, the UK’s Medicines and Healthcare Regulatory Agency, and COFEPRIS, the Mexican health regulator. This intelligence was gathered and analyzed for inspections from the second quarter of 2015 to the first quarter of 2016.

Inadequate investigation of out-of-specification results continues to be a top deficiency found by FDA inspectors as well. Of the 42 drug GMP warning letters sent to pharmaceutical manufacturers in FY 2015, 11 cited inadequate investigation of out-of-specification results under Part 211.192, making it the fifth leading deficiency in that year’s drug GMP warning letters.

In FY 2013, this deficiency was noted in 15 warning letters, and in 2014, it was noted in four warning letters. This blip was due to FDA’s focus on sterility practices at compounding pharmacies.

*From the editors of the Gold Sheet. Published online September 23, 2016*
FDA Investigators Finding Fewer Deficiencies For Visual Inspection Programs

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Greater clarity on visual inspection programs for parenteral drugs covered by the US Pharmacopeia’s new Chapter <790> may be the reason FDA investigators have been finding fewer problems over the past few years, industry officials said. Yet new observations are cropping up for inadequate sampling plans for visual inspections.


Shabushnig spoke at an interest group session, “GMP Links to Pharmacovigilance and Visual Inspection of Parenterals,” and along with John Ayres of Eli Lilly, he also spoke about recent recalls attributed to particle contamination; deficiencies seen in inspection reports; and how risk assessments can help focus resources on visual inspections for high-risk products.

Citing data from “GMP Trends,” Shabushnig said the number of 483 observations attributed to inadequate visual inspection programs has been decreasing the past few years.

This follows a dramatic uptick in observations in 2011-2013. In 2011, 13 visual inspection programs were noted in 483 observations. The number increased to 17 in 2012 and 22 in 2013 before dipping to 17 in 2014 but increasing to 18 in 2015; so far this year there have been six visual inspection observations.

This follows a dramatic uptick in observations in 2011-2013. In 2011, 13 visual inspection programs were noted in 483 observations. The number increased to 17 in 2012 and 22 in 2013 before dipping to 17 in 2014 but increasing to 18 in 2015; so far this year there have been six visual inspection observations.

“I could be cautiously optimistic that the number for 2016 is a bit down compared to the historical recent numbers. I have seen some improvements in this area and I think there is also greater clarity on what the expectations are. But there is more work to be done in this area. I think it is important to not overreact to one 483 observation but to look for recurring observations,” Shabushnig said.

GLOBAL TEMPLATE FOR VISUAL INSPECTIONS

Shabushnig said USP Chapter <790>, which establishes acceptable and unacceptable quality limits to particles, gives industry more guidance – and much needed clarity on setting up visual inspection programs.

USP <790>, which became an official chapter in August 2014, specifies conditions for the inspection for visible particles in injectables. It defines the requirement that parenteral drugs be “essentially free” of particles, a level stated in acceptable quality limit (AQL) acceptance sampling plans.

The chapter defines “essentially free” as a batch of parenteral product meeting an AQL of 0.65% or tighter based on process-specific capabilities. However, alternative sampling plans with equivalent or better protection are acceptable.

The chapter also outlines an inspection procedure of examining drugs “without magnification against a black background and against a white background with illumination that at the inspection point has an intensity of between 2.000 and 3.750 lux [lumens per square meter].”

The chapter is harmonized with the European Pharmacopoeia, or Ph. Eur; the Japanese Pharmacopoeia recently agreed to harmonize as well.

“I am also very happy to report that in the JP that was just published in Japanese earlier this year that their team has also adopted the same set of viewing conditions for the product, the same light intensity, and the light data background,” Shabushnig said.

Before USP <790> went into effect, there was much confusion about acceptable and unacceptable quality limits to guide industry in setting up visual inspection programs. Some manufacturers regarded visible particles as critical defects and had a zero tolerance threshold: They would not accept any lots with these defects.

Yet a zero tolerance policy simply is not practical, said Ayres, director of product...
safety assessments at Eli Lilly. Particles are derived from virtually every step of the manufacturing process: rubber particles come from stoppers and glass particles from vials.

“Every container contains particulate matter. You just have to live with it, either visible or sub-visible. If not you probably don’t have a product,” Ayres said.

COMMON OBSERVATIONS
From these inspection reports, Shabushnig culled common 483 observations related to visual inspections:

- Manufacturers need to establish a maximum allowable reject rate for batches containing visible particles;
- Manufacturers must control reinspection of products, including inspection conditions and the number of inspections permitted;
- Inspectors must be trained and the training must be documented;
- Inspectors must be periodically recertified;
- The training and certification conditions must align with routine 100% inspection conditions; and
- The training must address inspection fatigue during qualification.

Shabushnig noted some recent observations added to the list include:

- Manufacturers must conduct thorough investigations and identify particulate matter when performing investigations; and
- Manufacturers must use statistically sound sampling plans for AQL inspections.

NO ONE IS IMMUNE
Shabushnig also noted eight recalls attributed to visible particle contamination in the past few years:

- Sagent Pharmaceuticals’ recall of oxacillin injection in August 2016;
- Teva’s recall of amikacin sulfate injection in August 2016;
- Hospira’s April 2016 recall of magnesium sulfate injection;
- B. Braun Medical’s recall of 5% dextrose injection in March 2016;
- Mylan’s recall of cancer drug gemcitabine in June 2015;
- Baxter’s recall of two lots of intravenous solutions in July 2015;
- Alexion’s nationwide recall of Soliris (eculizumab) in June 2014; and
- Hospira’s recall of lidocaine HCl injection in July 2014.

Shabushnig said that from these recalls it is clear no one type of company is immune to particle contamination. “When you look at the companies it is not just big pharma or small pharma or offshore suppliers versus domestic suppliers or contract suppliers versus innovator firms. It is really across the board.”

The recalls also show particle contamination can emanate from a variety of sources. “If you look at the nature of the particles, you have some iron oxide, you have some glass particles, some general visible particles in solution and some in microbial growth so it is not just a single source but is a combination of things,” Shabushnig said.

PARTICLES DO NOT REPRESENT SAFETY RISK
Ayres said the recalls do not necessarily reflect that products with particle contamination are unsafe. He noted that in the US, several hundred million injectable doses of medicines are administered each year with “very, very rare cases” of adverse event reports associated with particle contamination.

Ayres said he is more concerned about sub-visible than visible particle contamination. “You have to remember if you are already seeing these things at the macro level, they have already been occurring at the sub-visible level.” He also said macroscopic particles are less threatening than sub-visible ones because they are too large to pass through the lumen of a needle.

Yet to ensure there is no impact to patient safety, manufacturers should conduct two types of risk assessment: characterize the particles and assess the intended therapeutic use.

Ayres said four factors should be evaluated in a particle characterization study:

- Measure the impact on sterility as a source of bioburden. “That to me is really the No. 1 thing we should be considering with respect to injectables.”
- Measure the particle’s composition and likelihood for organic or inorganic leachates. This means manufacturers should focus on the composition of the material. “We manufacture insulin and when you consider the fact that someone today diagnosed with diabetes can take three injections a day for the rest of their life, the materials of construction in the container closure systems, the fragmentation characteristics of discs and the repeated punctures, that is a big deal.”
- Consider the potential for the particle to promote intravascular occlusion, or obstructing the lumen of a vessel or to serve as a soft tissue or organ irritant.
- Consider the potential of the particles to express features that might induce or enhance an unexpected immune response.

In terms of particle characterization, Ayres sought to dispel a misperception that glass particles are different and riskier than particles derived from other sources. He said there is no evidence to support this.

“We put our product in glass and you can see that back in the good old days if you are going to have glass vials, you are going to have glass and you are going to have breakage on the line. From a safety standpoint it is almost invariably always sterile; it has gone through pyrogenation. It really doesn’t matter if you are injecting 50 microns if the particles are glass, metal or wood.”

Ayres said manufacturers, when doing risk assessments, should assess the intended patient population’s age and for co-morbid conditions and immune status.

Manufacturers should accord lower risk for drugs that are sterile and inert, as well as small volume products and those administered to healthy patients. Higher risk should be assigned to non-sterile products and those that are used in immunocompromised populations.

From the editors of the Gold Sheet. Published online September 28, 2016
Pfizer Keeps Hands On Consumer Product Wheel In Opting Against Split

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The next great potential hope for OTC switches remains under Pfizer Inc’s roof as the marketer of the blockbuster Lipitor (atorvastatin) keeps its consumer health business and all its other divisions together in a single company.

At this point, an OTC switch appears challenging, but a potential nonprescription version of the cholesterol treatment remains an attractive asset and Pfizer remains in the driver’s seat on any potential OTC path for Lipitor or any of its other Rx products.

The firm on Sept. 26 announced that it is best-positioned in its existing organization to generate growth and shareholder value and it will not pursue separating its innovative health and essential health divisions into two publicly traded companies. The innovative division includes the consumer health, oncology and vaccines businesses.

Pfizer’s statement, like analysts’ research notes following the announcement, did not mention the consumer health business, which includes OTC drugs and nutritional products, an indication the segment was not a large factor compared to the firm’s other businesses.

“I doubt that switch was a significant consideration in Pfizer’s decision on whether to split up the company. For a company of Pfizer’s size, even a highly successful switch would have a relatively modest impact on overall corporate earnings,” said Susan Lavine Coleman, a consultant on OTC switch proposals and other new drug applications.

Discussion on spinning off the consumer business along with oncology and vaccines began when Pfizer its structure with innovative and established divisions in 2013, but the firm has weighed leaving the consumer business since it re-entered the space with its 2009 acquisition of Wyeth.

In addition to former Wyeth brands including Advil (ibuprofen) analgesics and Centrum multivitamins, Pfizer’s consumer business markets proton pump inhibitor Nexium 24HR (esomeprazole/20mg), a switch it launched in 2014 under an OTC market license with innovator AstraZeneca PLC.

Lipitor’s indication for high cholesterol treatment is the most coveted indication yet to be available OTC. And cholesterol treatment is among the chronic conditions FDA encourages drug firms to target in Rx-to-OTC switch proposals.

And US Census Bureau research underscores the significance of moving Rx drugs to nonprescription for chronic conditions as well as to add ingredients to OTC monographs. A 2014 report, from research funded by the National Institutes of Health’s National Institute on Aging, showed that 92% of older consumers have a chronic condition and highlighted health and other trends among the older population, which is more than 40m and expected to more than double and become one-fifth of the US population by mid-century.

Switching a statin has been elusive for drug firms, however, including Pfizer. Its 1,200-subject actual use trial to simulate the OTC use of Lipitor 10 mg, completed in December 2014, did not meet its primary objectives of demonstrating patient compliance with the direction to check their low-density lipoprotein cholesterol level and, after checking, to take appropriate action based on test results.

Pfizer ended its Lipitor switch mission before filing a new drug application with FDA and the agency has rejected three previous statin switch NDAs due to the same problem the firm encountered – concerns about whether consumers could accurately self-select and safely use a statin.

Hurdles for In-House and Out-License Development

Right now, chances look slim for another switch attempt by the firm. Lavine Coleman, president of NCI Consulting in Moorestown, N.J., noted, “It can be more financially attractive to switch your own drug instead of selling or out-licensing OTC rights, assuming that the switch is ultimately approved by FDA and that the drug is successful in OTC market.” But this would require newly designed studies and additional investments which could be used “for near-term and/or less risky opportunities.”

On the other hand, impressed with an offer from another firm, Pfizer could opt to out-license OTC rights to the product.

“For the high risk/high reward switches, Rx companies can sometimes better achieve their overall business objectives by auctioning OTC rights. This is especially true for first-in-indication switches that may be big OTC opportunities but entail a lot of risk and investment,” Lavine Coleman said.

The list is short, though, for potential buyers for OTC rights to Lipitor or any other Rx ingredient that would be a first in the nonprescription product aisles. Smaller firms focused on OTCs probably don’t have the budget, and Pfizer’s big pharma competitors might not have the same interest.

“There aren’t many pure-play OTC companies pursuing switch. Among companies with Rx and OTC divisions, there are big differences today in company willingness to invest in switch,” Lavine Coleman observed.

She added that while some pharma expect spending for switch investments to come from their OTC division budgets, others will allow the division so wiggle room on margins to invest in switch.

Analysts had expected Pfizer would split off its innovative and established divisions, especially after the failure in April of its planned merger with Allergan PLC that would have brought a tax-inversion through re-incorporating in Ireland.
Perrigo Deal Makes Extraction-Resistant PSE A Two-Player Competition

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Perrigo Co. PLC, gains exclusive rights to a tamper-resistant pseudoephedrine formulation for private label distribution and to market a branded product also made with the technology, under an agreement announced Sept. 27 with Highland Pharmaceuticals LLC.

With the deal, Perrigo obtains the only tamper-resistant PSE formulation still available for licensing in the US. The second firm in the space, Acura Pharmaceuticals Inc., licensed its technology to Bayer HealthCare LLC in June 2015. The Perrigo/Highland deal makes the US consumer tamper-resistant pseudoephedrine market a two-company space, but also puts Perrigo in the lead in reaching purchasers.

Perrigo is licensing Highland’s Tarex lipid-based drug delivery system developed to prevent extracting PSE and will use Tarex in PSE products it makes, expanding the already extensive portfolio of OTC drugs it makes to be sold as private label or store brand products.

It also is licensing the Zephrex-D (PSE 30 mg) product made with Tarex and currently marketed by Highland’s Westport Pharmaceuticals LLC business. Zephrex-D will be Perrigo’s first product in the US branded consumer health market and immediate distribution is planned. Zephrex-D has been proven to be more than 98% effective in block extraction of PSE, which is used to make methamphetamine, the firm said.

Perrigo and privately held Highland did not disclose financial terms for their agreement, and Perrigo has yet to file a report describing the deal to the Securities and Exchange Commission. Perrigo’s share price edged up about 1.09% to $96.77 on the date of the deal’s announcement; shareholders and analysts have suggested divestments, rather than Perrigo’s consistently favored acquisitions approach, to improve share value.

Still, Perrigo plays to its strength with the Highland deal and could make more of the products brought in due to its significantly larger distribution network. “We are committed to leveraging the Tarex technology to extend our line of meth-resistant pseudoephedrine products in the future,” Jeff Needham president of Perrigo’s Consumer Healthcare - Americas business, said in the firm’s release.

St. Louis-based Highland is focused more on developing formulations resistant to PSE or opioid ingredient extraction than on marketing finished products and has much less distribution capacity than Perrigo. Highland’s Sentinel Pharmaceuticals LLC subsidiary will continue to develop tamper-resistant formulations for opioid drugs using Tarex.

The new deal resembles in some ways the Bayer/Acura relationship.

Like Highland, Palatine, Ill.-based Acura markets a branded nonprescription product and has licensed its tamper-resistant technology to a firm with much larger manufacturing and marketing capacity. Bayer HealthCare markets the antihistamine Claritin-D (PSE/loratadine), is working with Acura to develop a product using the Impede technology for the US market and can negotiate for a worldwide license for additional products.

Acura continues to market its Nexafed 30mg immediate-release PSE product and a Sinus Pressure + Pain (PSE 30mg/acetaminophen 325mg) version of the brand.

The agreement gave the Bayer AG business a chance to become the first big pharma firm to use a tamper-resistant claim for nonprescription pseudoephedrine products – but it has yet to introduce a product using Impede and it will be beat to the finish line as Perrigo immediately begins marketing Zephrex-D while also working on Tarex-formulated products of its own.

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NOT EXTRACTION-PROOF, BUT RESISTANT

None of the firms, though, can make an “extraction-proof” claim for a PSE product.

All nonprescription PSE-containing products are sold behind-the-counter under the Combat Methamphetamine Act of 2006. The act allows the Drug Enforcement Administration to grant front-of-counter waivers to nonprescription PSE products determined to be extraction-proof, but other than Bayer and Perrigo, no other major pharma firms...
have shown interest in developing products with tamper-resistant formulations.

Highland and Acura both have planned to make extraction-proof claims, but tests have shown their formulations would not prevent extraction of some PSE. The technologies so far support labeling as tamper- or extraction-resistant, but none have prevented removal of enough PSE to earn extraction-proof approval.

Westport briefly marketed Zephrex-D product in 2012 with the claim until the DEA advised the firm that DEA chemists produced meth with PSE extracted from its formulation. Still, Acura and Highland point out their products are stronger deterrents to meth cooks than traditionally formulated PSE products. More of their products would be needed to remove the same amount of PSE that can be extracted from traditional formulations.

Two states – Oregon and Mississippi – require prescriptions for all PSE products and other states and some local governments have imposed more stringent monthly and daily purchase limits than the federal law set.

In addition to licensing its Impede PSE formulation to Bayer HealthCare, Acura is developing a tamper-resistant formulation for opioid products.

From the editors of the Tan Sheet. Published online September 27, 2016

GDUFA II: ANDAs, Not Facilities Will Govern Revenue

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Generic drug user fee revenue during the second program cycle primarily will be generated from ANDA submissions, rather than facilities, to create a more equitable divide of the revenue burden.

Manufacturers will pay an annual “program fee,” but GDUFA II “will be funded at a level commensurate with the amount of work associated with incoming ANDAs, since ANDAs are the primary workload driver of GDUFA,” FDA wrote in a Federal Register notice published Sept. 26.

FDA said in the notice that no facility or sponsor will pay an annual fee until “an ANDA in which it is listed is approved.”

The new program fee appears to be replacing what had been called the facility fee.

In the notice, FDA states “this annual fee will help offset the fluctuations in application fees from one year to another.” ANDA review and approval has been the Office of Generic Drugs’ most watched and criticized performance metric.

FDA has seen its rate of approvals improve over the last year, although submissions also are increasing.

However, the total number of submissions per year cannot be predicted easily, unlike facility counts. Submissions and FDA actions have outperformed estimates in previous years.

ANDA sponsors will be divided into three tiers based on ANDA ownership and pay the program fee based on the number of approved ANDAs they and their affiliates own.

FDA said in the notice that industry determined the tier cutoffs, which “are meant to reflect a firm’s size, position in the market, and reliance on the program.”

Annual and one-time fees also were discussed as potential options for the new fee structure during GDUFA II negotiations.

Prior approval supplement fees were eliminated, according to the notice.

FDA also created a program fee for the next prescription drug user fee program cycle, as well as eliminated supplement fees.

The Federal Register notice announced an Oct. 21 public meeting at FDA’s White Oak headquarters to solicit comments on the GDUFA II agreement.

The agreement also includes an eight-month priority review pathway for some ANDAs.

The commitment letter, which contains the details of the agreement between FDA and industry to reauthorize the program, has not been released.

ANDA FEES TO INCREASE?

The new fee structure may push ANDA submission fees significantly higher and facility fees lower during GDUFA II, although the notice does not provide more detail on how fees will be calculated.

When GDUFA I launched in 2012, the agency and industry structured the fees to generate the majority of revenue from annual facility fees.

In FY 2017, the final year of the first program cycle, fees for finished dosage form facilities are expected to comprise 56% of the $323m to be generated and are by far the most expensive. Fees for active pharmaceutical ingredient manufacturers are estimated to comprise another 14% of the total (see graphic).

ANDA and prior approval supplement fees are expected to comprise 24% of the total.

The reasoning for depending on facilities for most of the revenue during GDUFA I was to ensure a dependable and consistent funding stream.
But complaints quickly emerged from manufacturers, who said the fees were unaffordable and sometimes even more than the income sponsors were expecting to generate from the products.

**NO WAIVER, BUT STILL SMALL BUSINESS RELIEF**
Small businesses received the relief they demanded in the new agreement, although it is not the waiver or discount that had been envisioned.

FDA said in the notice that no facility or sponsor will pay an annual fee until "an ANDA in which it is listed is approved." That change is intended to attack one of the primary complaints from small businesses, as well as account for the agency's sometimes lengthy ANDA approval times.

Under the existing fee structure, facilities pay the annual fee if they are listed in an ANDA even if it is not approved. For facilities looking to enter the generics business, that can be a hardship.

And since OGD has been taking several years to approve some ANDAs, a manufacturer new to the sector could pay a substantial amount of fees before marketing any products.

Most ANDAs require multiple review cycles, in some cases four or more to gain approval.

The GDUFA II agreement also makes provisions specifically for contract manufacturers, since they generally are "small businesses that are hired by ANDA sponsors to manufacture their generic drugs," according to the notice.

Contract manufacturing organizations (CMOs) will pay one-third of the annual fee charged to firms manufacturing under ANDAs in facilities they or their affiliates own, according to the notice.

"Some CMOs have kept facilities out of the generic space because they and their potential sponsors did not want to incur multiple years of facility fees without an approved ANDA in that site," Roth told the Pink Sheet.

PBOA argued that contract manufacturers paid full facility fees even though many do not work in the industry exclusively.

GDUFA II, along with reauthorizations for the biosimilar and prescription drug user fees, are expected to be sent to Congress in January 2017 and incorporated into must-pass legislation.

The programs will expire in October 2017 absent an extension.

*Published online September 26, 2016*
Japan Approvals Include Keytruda,
First Asia Nod for Iclusig
IAN HAYDOCK ian.haydock@informa.com

Ariad Pharmaceuticals Inc’s Iclusig (ponatinib) has been approved in Japan for second-line use in chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) through Asian licensee Otsuka Pharmaceutical Co. Ltd.

A 15mg tablet formulation of the oral kinase inhibitor is indicated for CML patients resistant or intolerant to previous drug treatment, and patients with previously treated recurrent or refractory Philadelphia chromosome-positive ALL.

The regulatory clearance triggers a $10m milestone payment to Ariad by Otsuka, which under a December 2014 agreement holds rights to Iclusig in South Korea and Taiwan - where the product is currently awaiting approval - and a range of other countries and regions in Asia.

“Japan represents a large market opportunity for Iclusig and its first approval in Asia,” Ariad president and CEO Paris Panayiotopoulos noted in a statement. The product has orphan status in the country and the approval comes around nine months after a regulatory submission in January this year.

It was supported by a local 35-patient Phase I/II study in patients failing tyrosine kinase inhibitor therapy, in which 65% of the 17 chronic phase patients achieved the primary efficacy endpoint of major cytogenic response, as well as by data from the international PACE pivotal trial with ponatinib.

Iclusig is already approved in the US (in 2012), the EU (2013) and in several other countries.

**EARLY ACCESS PROGRAM**

Ponatinib targets native and isoform BCR-ABL, an abnormal tyrosine kinase expressed in CML and Ph+ ALL that can confer drug resistance, particularly through the specific T315i mutation. Standard first-line tyrosine kinase inhibitors include dasatinib (Bristol-Myers Squibb Co.’s Sprycel) and nilotinib (Novartis AG’s Tasigna).

In a rare move in Japan, Otsuka said that it would provide Iclusig free of charge to patients through an early access program until reimbursement is secured under Japan’s national health insurance system. The scheme will be offered at sites that participated in the local clinical trial with the product and which also agree to supply the drug.

Following product approval, new drugs are typically included in the reimbursement tariff within several months, but pricing (which allows full commercial launch) can in some cases be delayed by ongoing official discussions.

### New Products Approved in Japan On Sept.28

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>COMPANY</th>
<th>INDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilanoa (bilstane)</td>
<td>Taiho Pharmaceutical Co. Ltd. (licensed from Faes Farma SA, to be co-marketed by Meiji Seika Pharma Co. Ltd.)</td>
<td>Allergic rhinitis, urticaria and itching related to dermal disorders</td>
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<tr>
<td>Brilinta (ticagrelor)</td>
<td>AstraZeneca</td>
<td>Angina/ stroke prevention</td>
</tr>
<tr>
<td>Desalex (desloratadine)</td>
<td>MSD</td>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>Empliciti (elotuzumab)</td>
<td>BMS</td>
<td>Refractory/recurrent multiple myeloma</td>
</tr>
<tr>
<td>Idelvion (rDNA Factor IX)</td>
<td>CSL Behring</td>
<td>Hemophilia B</td>
</tr>
<tr>
<td>Juxtapid (lomitapide)</td>
<td>Aegerion Pharmaceuticals Inc.</td>
<td>Homozygous familial hypercholesterolemia</td>
</tr>
<tr>
<td>Ovidrel (choriogonadotropin alfa)</td>
<td>Merck Serono SA</td>
<td>Anovulation</td>
</tr>
<tr>
<td>Prizubind (idarucizumab)</td>
<td>Boehringer Ingelheim GMBH</td>
<td>Reversal of dabigatran</td>
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<tr>
<td>Signifor LAR (pasireotide)</td>
<td>Novartis</td>
<td>Acromegaly</td>
</tr>
<tr>
<td>Uptav (selexipag)</td>
<td>Nippon Shinyaku Co. Ltd. (partnered with Actelion Pharmaceuticals Ltd.)</td>
<td>Pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Xifanxan (rifaximin)</td>
<td>ASKA Pharmaceutical Co. Ltd. (Alfa Wassermann SPA)</td>
<td>Diarrhea-predominant irritable bowel syndrome</td>
</tr>
<tr>
<td>Zapatier (grazoprevir plus elbasvir)</td>
<td>MSD</td>
<td>Hepatitis C</td>
</tr>
</tbody>
</table>

Source: Ministry of Health, Labor and Welfare.
KEYTRUDA FOR MELANOMA
Also approved was Merck Sharp & Dohme Ltd’s Keytruda (pembrolizumab) for its first local indication of metastatic melanoma. The PD-1-targeting antibody is also under review in Japan for metastatic non-small cell lung cancer (NSCLC) and in development for a broad range of indications including bladder, breast, and esophageal cancer, and has been granted “Sakigake” (breakthrough) status for advanced gastric cancer.

Melanoma affects around 4,000 people and causes some 600 deaths in Japan every year, MSD’s local subsidiary noted.

Ono Pharmaceutical Co. Ltd./BMS’s rival anti-PD-1 product Opdivo (nivolumab) is already marketed for the same relatively small indication in Japan, but its main sales expansion has come through use in NSCLC. So much so in fact that the high cost of the drug was one factor behind a sharp rise in Japan’s healthcare costs last fiscal year.

With Keytruda now moving through the price-setting process, its reimbursement level - which could be set using Opdivo as a comparator - is likely to generate attention as the new wave of immuno-oncology therapies gathers commercial momentum in Japan.

MSD also gained approvals for several other drugs, as did AstraZeneca PLC for its platelet aggregation inhibitor Brilinta (ticagrelor).

Aegerion described the clearance of Juxtapid as “a significant milestone”, noting that since the drug was granted orphan status for homozygous familial hypercholesterolemia in the country in 2013 it has been working to establish awareness of the rare genetic disorder, which impairs LDL-C removal.

The approval was based on a small (nine-patient) pivotal study in Japan.

NEW COMBINATIONS
The Ministry of Health, Labor and Welfare also cleared a number of new combination products for marketing, including Takeda Pharmaceutical Co. Ltd’s Inisync, a once-daily fixed-dose formulation of the DPP-4 inhibitor alogliptin (25mg) with metformin (500mg) for the treatment of type 2 diabetes.

Boehringer Ingelheim’s once-daily antihypertensive Micatrio (telmisartan 80mg, amlodipine 5mg and hydrochlorothiazide 12.5mg) will become the first triple combination for high blood pressure to become available in Japan, and will be distributed and co-promoted by Astellas Pharma Inc.

Otsuka’s ophthalmic combination Mike-luna, comprising the beta-blocker carteolol and the prostaglandin analogue latanoprost, was approved for glaucoma and ocular hypertension and will be co-promoted with eye care specialist Senju Pharmaceutical Co. Ltd.

New Indications
Rounding out the approvals were a number new indications that included AbbVie Inc.’s Humira (adalimumab) for non-infectious uveitis, and Otsuka’s atypical antipsychotic Abilify (aripiprazole) for irritability associated with pediatric autism spectrum disorder.

Humira, which is distributed and co-promoted by Eisai Co. Ltd., becomes the first biologic therapy in Japan for intermediate, posterior and panuveitis regardless of underlying disease.

From the editors of PharmAsia News. Published online September 26, 2016.

**FDA’s NDA And BLA Approvals**
Below are FDA’s original approvals of NDAs and BLAs issued in the past week. Please see key below chart for a guide to frequently used abbreviations

<table>
<thead>
<tr>
<th>SPONSOR</th>
<th>PRODUCT</th>
<th>INDICATION</th>
<th>CODE</th>
<th>APPROVAL DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Drugs</td>
<td></td>
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<tr>
<td>Janssen</td>
<td>Stelara (ustekinumab)</td>
<td>130 mg/26 mL injectable formulation of the anti-inflammatory for adults with moderately to severely active Crohn’s disease</td>
<td>3</td>
<td>9/23/2016</td>
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<tr>
<td>New Biologics</td>
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<tr>
<td>Amgen</td>
<td>Amjevita (adalimumab-atto)</td>
<td>Biosimilar to Humira for treating rheumatoid arthritis; juvenile idiopathic arthritis; psoriatic arthritis; ankylosing spondylitis; adult Crohn’s disease; ulcerative colitis; and plaque psoriasis</td>
<td>9/23/2016</td>
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KEY TO ABBREVIATIONS

<table>
<thead>
<tr>
<th>Review Classifications</th>
<th>NDA Chemical Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>P: Priority review</td>
<td>1: New molecular entity (NME); 7: Drug already marketed without an approved NDA; 9: New indication submitted as distinct NDA – consolidated with original NDA</td>
</tr>
<tr>
<td>S: Standard review</td>
<td>2: New active ingredient; 8: OTC (over-the-counter) switch</td>
</tr>
<tr>
<td>O: Orphan Drug</td>
<td>3: New dosage form; 10: New indication submitted as distinct NDA – not consolidated with original NDA</td>
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<tr>
<td></td>
<td>4: New Combination; 5: New formulation or new manufacturer; 6: New indication</td>
</tr>
<tr>
<td></td>
<td>11: New indication submitted as distinct NDA – separately approved</td>
</tr>
<tr>
<td></td>
<td>12: New indication submitted as a separate NDA for a new indication not submitted as a distinct NDA</td>
</tr>
</tbody>
</table>

|          | 4: New Combination; 5: New formulation or new manufacturer; 6: New indication; 10: New indication submitted as distinct NDA – not consolidated with original NDA |
|          | 11: New indication submitted as distinct NDA – separately approved |
|          | 12: New indication submitted as a separate NDA for a new indication not submitted as a distinct NDA |

|          | 4: New Combination; 5: New formulation or new manufacturer; 6: New indication; 10: New indication submitted as distinct NDA – not consolidated with original NDA |
|          | 11: New indication submitted as distinct NDA – separately approved |
|          | 12: New indication submitted as a separate NDA for a new indication not submitted as a distinct NDA |
# Recent And Upcoming FDA Advisory Committee Meetings

<table>
<thead>
<tr>
<th>TOPIC</th>
<th>ADVISORY COMMITTEE</th>
<th>DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naloxone products intended for use in the community, specifically: the most appropriate dose or doses to reverse effects of life-threatening opioid overdose in all ages; the role of having multiple doses available in this setting; criteria prescribers will use to select the most appropriate dose in advance of an opioid overdose event and labeling to inform this decision if multiple doses are available</td>
<td>Anesthetic and Analgesic Drug Products; Drug Safety and Risk Management</td>
<td>Oct. 5</td>
</tr>
<tr>
<td>Selection of strains to be included in an influenza virus vaccine for the 2017 southern hemisphere influenza season</td>
<td>Vaccines and Related Biological Products</td>
<td>Oct. 13 (teleconference)</td>
</tr>
<tr>
<td>Serenity Pharmaceuticals’ desmopressin 0.75 mcg/0.1 ml and 1.5 mcg/0.1 ml nasal spray for treatment of adult-onset nocturia</td>
<td>Bone, Reproductive and Urologic Drugs</td>
<td>Oct. 19</td>
</tr>
<tr>
<td>Updates on research programs in the Laboratory of Immunobiochemistry of the Division of Bacterial, Parasitic and Allergenic Products in CBER’s Office of Vaccines Research and Review (open session); intramural research program reports and recommendations on personnel staffing decisions (closed session)</td>
<td>Allergenic Products</td>
<td>Oct. 27 (teleconference)</td>
</tr>
<tr>
<td>Cempra Pharmaceuticals’ solithromycin capsules and injection for treatment of community-acquired bacterial pneumonia</td>
<td>Antimicrobial Drugs</td>
<td>Nov. 4</td>
</tr>
<tr>
<td>Recommendations on FDA’s draft Strategic Plan for Risk Communication and Health Literacy; presentations on some of FDA’s external communications and how these relate to the draft strategic plan</td>
<td>Risk Communication</td>
<td>Nov. 7</td>
</tr>
<tr>
<td>Appropriate clinical trial design features, including acceptable endpoints for demonstrating clinical benefit, for drugs intended to treat secondary hypogonadism while preserving or improving testicular function, including spermatogenesis</td>
<td>Bone, Reproductive and Urologic Drugs</td>
<td>Dec. 6</td>
</tr>
</tbody>
</table>
Select clinical trial sites with pinpoint accuracy.

1. Match patient populations of interest with qualified investigators for faster, more successful clinical trials.

2. Get insight into diseased population size to drive country, site and experienced investigator selections for maximum feasibility and rapid decision-making.

Visit https://goo.gl/DOHY7N to find out more.
The BIO Investor Forum is an international biotech investor conference focused on early and established private companies as well as emerging public companies. Now in its 15th year, this elite event brings together angel, venture capital, venture philanthropy, private equity and public investors, research analysts and industry executives in a collaborative setting to explore development and investment opportunities in life sciences.

**Conference features:**

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- Fireside Chats and expert-led panel discussions on the latest market and investment opportunities with emphasis on drug and technology development.
- More than 1,700 One-on-One Partnering™ meetings.
- Buzz of BIO competition recognizing “Early Stage Entrepreneurs” and “Late Stage Leaders.”
- The BIO SPARK Showcase featuring drug development programs that are ready for partnering or venture funding.

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