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# Choice Of Regulatory Pathway Is Key Inflection Point In Drug Reviews

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The proliferation of regulatory pathways gives FDA a powerful way to set priorities and shape drug development, an overview of the Pink Sheet's Drug Review Profile series shows.

Multiple reauthorizations of the Prescription Drug User Fee Act and decades of regulatory experience have built a complicated edifice of pathways to approval, especially for drugs for unmet needs. Analyzing the agency's review documents shows that FDA uses its role as keeper of the keys to influence sponsors to address the agency's priorities and concerns before approval.

**DRUG REVIEW PROFILE**

The designations and incentives offered through FDA range from the venerable priority and standard review classifications through accelerated approval and fast track to the new breakthrough therapy designation (*for an overview of FDA's expedited approval programs, see "A User Guide To FDA's Expedited Programs For Serious Conditions" — "The Pink Sheet," June 16, 2014*).

Our Drug Review Profiles, launched in the Pink Sheet a year ago, look closely at FDA review documents each month to provide insights into FDA decision-making. The anniversary gives a chance to take stock of themes and highlights of the series. (*In an upcoming issue, the Pink Sheet will look at the Drug Review Profile for the first biosimilar to clear FDA, Zarxio, and how those issues are playing out in biosimilar development*).

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*Our Drug Review Profiles, which look closely at FDA review documents each month to provide insights into FDA decision-making, have reached their first anniversary in the Pink Sheet. Look online for a list of article highlights from the past year.*

## THE APPEAL OF ACCELERATED APPROVAL

The accelerated approval pathway appears to be commonly discussed as an option for products where FDA feels the evidence is promising but falls short of regulatory standards for regular approval. Accelerated approval allows for approval on the basis of a surrogate endpoint that is considered to predict clinical benefit, which must be confirmed in a trial completed post-marketing.

FDA used accelerated approval to clear **Pfizer Inc.**'s breast cancer therapy *Ibrance* (palbociclib) on the basis of positive results from a Phase I/II study, PALOMA 1, that had not been designed as a pivotal trial.

"Given the magnitude of the benefit conferred, FDA agreed to review the data and results from PALOMA 1," Division Director Amna Ibrahim explained in a Feb. 3 summary review. The Phase III PALOMA 2 trial would be the confirmatory study required for accelerated approval, not the pivotal trial as originally envisioned.

"Accelerated approval would provide palbociclib to patients approximately two years earlier than awaiting the final Phase III trial results," the clinical review stated.

Ibrance's positive early clinical trial data also earned the oncologic a breakthrough therapy designation. The "all hands on deck" commitment of resources that breakthrough status brings was vital to the labor-intensive review, which required an extensive array of statistical analyses and meetings with the sponsor (*"Ibrance Illustrates Heavy FDA Workload For 'Breakthrough' Reviews" — "The Pink Sheet," July 20, 2015*).

Accelerated approval was a lifeline for **Novartis AG**'s *Farydak* (panobinostat) as a third-line multiple myeloma therapy. The drug did not show a benefit in relapsed multiple myeloma patients that clearly outweighed the drug's high toxicity, which could have doomed it. FDA, however, moved the NDA from the regular to the accelerated approval pathway, in order to access the regulatory flexibility allowed for expedited review products (*"FDA Used Regulatory Loophole To Save Novartis' Farydak" — "The Pink Sheet," Aug. 17, 2015*).

FDA also used the requirement for confirmatory studies of accelerated approval drugs to essentially write an alternative de-

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velopment plan to remedy the Farydak NDA's poor dose finding.

FDA considered using accelerated approval for **Amgen Inc.**'s viral oncolytic *Imlygic*, which was submitted with pivotal studies using an endpoint – durable response rate – that is less relevant today than it was when the trial started in 2009. The approval of Bristol's immunotherapy *Yervoy* in 2011 kicked off a revolution in melanoma treatment that changed the goals for therapy. Some reviewers were concerned that DRR could not stand on its own as a clinically meaningful measure. Given the availability of products that have demonstrated an overall survival benefit, DRR could only be considered a surrogate endpoint, they said.

Ultimately, FDA chose to grant Imlygic full approval. "There may not be metrics that adequately capture the value of watching a tumor disappear, but I was persuaded by the patients, their caregivers, and the physicians who served on the advisory committee that DRR is clinically meaningful," Center for Biologics Evaluation and Research Division of Clinical Evaluation and Pharmacology/Toxicology Director Wilson Bryan explained (*"Patient Voices Swayed FDA's* Imlygic *Review Team" — "The Pink Sheet," April 25, 2016*).

Accelerated approval was also floated as an option to expedite clearance of **Allergan PLC** 's antibacterial *Avycaz* (ceftazidime and avibactam). Pre-NDA meeting minutes show the agency concluding instead that "there is no surrogate endpoint that is reasonably likely to predict clinical benefit for CAZ-AVI."

Avycaz had earned Qualified Infectious Disease Product (QIDP) status, which ensures priority review as well as providing marketing exclusivity incentives in an effort to encourage and expedite approval of new anti-infectives.

The Avycaz review suggests that FDA found room in its existing authorities to approve expeditiously an antibiotic for restricted use.

Instead of accelerated approval, FDA directed the Avycaz sponsors to the 505(b)(2) NDA filing pathway. Such filings, sometimes called "paper NDAs," are more commonly used for new formulations of approved molecules than for new molecular entities; the pathway allows a sponsor to reference safety and efficacy data for a molecule that has already been approved in another form, instead of conducting full-fledged Phase III trials.

Avycaz could access the efficiencies of the 505(b)(2) pathway because the antibiotic component of the product, ceftazidime, was previously approved as a standalone product. The novel component of Avycaz, the beta lactamase inhibitor avibactam, thwarts the development of bacterial resistance to the antibiotic.

Congress is considering further incentives for antibiotic development, including a formal limited population antibiotic development (LPAD) program. The Avycaz review suggests that FDA found room in its existing authorities to approve expeditiously an antibiotic for restricted use (*"Flexibility Or Formal Pathway?* Avycaz *Suggests FDA Doesn't Need Congress To Expedite Limited Use Antibiotics" — "The Pink Sheet," May 18, 2015*).

## EVERYBODY WANTS PRIORITY REVIEW

The shorter review timeline for priority review drugs – six months vs. 10 months for standard review (NMEs and novel biologics also add a two-month filing review period) – makes the designation a tempting target for drug developers, especially those in competitive markets where a few months of sales can be commercially significant.

FDA, however, can be strict about what qualifies for priority review, recent Drug Review Profiles show. (*Look at the Pink Sheet online for links to all the Drug Review Profile stories for the past year.)*

As the first two PCSK9 inhibitors raced toward the market, the sponsors of both *Praluent* (**Sanofi** and **Regeneron Pharmaceuticals Inc.**) and *Repatha* (**Amgen Inc.**) requested priority review for the new class of cholesterol-lowering medication (*"PCSK9 Sponsors Looked For Regulatory Advantages In Race To Market" — "The Pink Sheet," Dec. 21, 2015*).

The priority review designation is a tempting target for drug developers, especially in competitive markets, but recent Drug Review Profiles show FDA can be strict about what qualifies for priority review.

Amgen cited data for Repatha (evolocumab) in homozygous familial hypercholesterolemia (HoFH), a condition where Repatha received an orphan drug designation. FDA, however, told the company that "the observed treatment effect on LDL-cholesterol among patients with HoFH was simply not compelling enough compared with alternative therapies to warrant a priority review."

Sanofi and Regeneron asserted that Praluent (alirocumab) should receive priority review as "a first-in-class therapeutic with demonstrated safety and efficacy in patients suffering from hypercholesterolemia (familial and non-familial) who are unable to achieve sufficient lowering of their LDL-C with currently available lipid lowering therapies (including statins)," according to meeting minutes. "As such it treats a serious condition (elevated LDL-C in patients with increased CV risk) and, if approved, would provide a significant improvement in effectiveness," the sponsors maintained.

FDA also rejected that plea for priority review, and Sanofi and Regeneron used a priority review voucher bought from **BioMarin Pharmaceutical Inc.** to get their drug on the market before Amgen.

**Daiichi Sankyo Co. Ltd.** sought priority review for its novel oral anticoagulant (NOAC) *Savaysa* (edoxaban) despite being the fourth product in the class, review documents show. In response, Cardio-Renal Division Director Norman Stockbridge "explained that convincing the division that a priority review was warranted would be difficult because of the prior approvals of drugs in this class that were superior to warfarin" (*"Savaysa Couldn't Get Two Indications Out Of One Trial" — "The Pink Sheet," April 27, 2015*).

**Kythera Biopharmaceuticals Inc.** (now part of Allergan) unsuccessfully tried to get priority review for the chin fat drug *Kybella* (deoxycholic acid) on the basis of safety concerns about pharmacy compounding. While the agency acknowledged the risks associated with loosely regulated compounded versions of deoxycholic acid, it rejected Kythera's request because regulations limit priority review to treatments for serious diseases or conditions, which the agency said are "associated with morbidity that has substantial impact on day-to-day functioning" – a standard that is not met by moderate to severe convexity or fullness associated with submental fat (*"Chin Fat Not A 'Serious Condition' Worthy Of Priority Review, FDA Says" — "The Pink Sheet," Sep. 21, 2015*).

## THE LIMITS OF INCENTIVES

With the next round of PDUFA reauthorization looming, new ideas about how to get medically important drugs to patients as quickly as possible are bouncing around Washington.

FDA has demonstrated, with several years of record novel approval totals and rising first-cycle approval rates, that it is already capable of applying regulatory flexibility and creativity under existing authorities. The Drug Review Profile series amply illustrates the efforts made across the agency to ensure safety and efficacy while at the same time speeding review of treatments for unmet medical needs.

But that stellar review performance has come at a cost for FDA in terms of potentially unsustainable workloads, especially given the lack of dedicated user fee funding for the popular breakthrough therapy program. The Drug Review Profile series also shows that the agency is selective about when to use expedited programs, disappointing some sponsors in order to more effectively harness the agency's limited resources for medical advances.

REGULATORY UPDATE

# REMS Assessment Challenges Shine Through In Opioids Review

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Eight years after FDA's authority to require Risk Evaluation and Mitigation Strategies took effect, the agency and industry are still grappling with how best to assess the programs' effectiveness.

So too are FDA's external advisors, who during a two-day review of the REMS for extended-release/long-acting opioids were underwhelmed by product sponsors' assessment data. Some even questioned whether the massive risk management program's impact can be measured.

The ER/LA REMS assessments included patient and prescriber surveys, surveillance and drug utilization data. Panelists pointed to methodological shortcomings and said the various instruments were not capable of measuring an effect on some of the REMS' key goals, including a reduction in inappropriate prescribing.

Committee members expressed frustration that the assessment strategies were not better thought out, and they said better objective measures were needed to evaluate effectiveness. Suggestions included longitudinal observational studies comparing prescriber behaviors pre- and post-training, and a randomized controlled trial to determine if the REMS is making any difference on prescribing behavior and safety outcomes for patients.

"We clearly need a better evaluation strategy to figure out whether this is worth the money," said Niteesh Choudhry, a health services researcher at Harvard.

> "If I had any reluctance whatsoever in recommending mandatory training or expanding training to IR formulations, it would hedge on the fact that we're really looking at an inadequately evaluated system" – Columbia University's Emala

Comments from FDA staff and the product sponsors suggested both sides are learning as they go about the capabilities for assessing REMS programs, including new opportunities available through electronic databases.

Some clarity around FDA's thinking on assessments and best practices may soon be coming. The Center for Drug Evaluation and Research's guidance agenda for 2016 includes plans for documents on survey methodologies to assess REMS goal-related knowledge, and planning and reporting of REMS assessments.

The committee unanimously supported adding immediate-release opioids to the REMS. Although prescriber education under the REMS is currently voluntary, all but one panelist favored making that education mandatory, preferably through linkage to Drug Enforcement Administration registration and renewal to prescribe controlled substances (*"Restrictive REMS Is Least Favored Path For Opioid Prescriber Education" — "The Pink Sheet," May 9, 2016*).

However, some of the experts conceded that these proposed changes to the REMS were not well informed by the current evaluation of the program's effectiveness.

"If I had any reluctance whatsoever in recommending mandatory training or expanding training to IR formulations, it would hedge on the fact that we're really looking at an inadequately evaluated system at this point," Columbia University anesthesiologist Charles Emala said.

## SHORTCOMING IN SURVEYS, SURVEILLANCE DATA

Approved in July 2012, the ER/LA REMS is the largest risk management program the agency has required under the FDA Amendments Act's drug safety authorities, which took effect in March 2008. The program's core feature is voluntary prescriber education, which is conducted through industry grants to accredited continuing education providers. It is the first REMS to use accredited CE as a primary tool.

FDA convened two advisory committees – Drug Safety and Risk Management, and Anesthetic and Analgesic Drug Products – to review the third assessment submitted under the REMS and the first one with performance targets for prescriber completion of voluntary training. The assessment showed the number of completers fell well short of the 80,000-prescriber goal (*"Opioid Product Sponsors Eye REMS Fixes To Boost Prescriber Education Uptake" — "The Pink Sheet" DAILY, April 29, 2016*).

Overall, FDA reviewers concluded the assessment findings "show mixed results that make it difficult to draw conclusions regarding the success of the program."

The review identified a number of shortcomings with the assessments (*"Opioid REMS: FDA Sees No Clear Verdict On Risk Management Program's Impact" — "The Pink Sheet" DAILY, April 27, 2016*). Although the prescriber surveys sought to evaluate knowledge before and after REMS training, the product sponsors did not attempt to survey the same individual prescribers or to make respondents of the surveys comparable, FDA said. However, sponsors said their ability to assess behavior change following REMS-compliant education was limited because they did not have access to information on which prescribers completed the training (*"Opioid Continuing Education Rules Hamper REMS Assessments" — "The Pink Sheet" DAILY, May 3, 2016*).

The prescriber and patient surveys showed a good understanding of the key risk messages, FDA said. However, the agency raised generalizability as a concern for all the surveys, noting for example that prescribers choosing to take the CE training may differ from the ER/LA opioid prescriber population in general. All the surveys were convenience samples, and the results may be biased, FDA said.

Surveillance data on misuse, abuse, overdose, addiction and death suggested mixed results, FDA said. There were decreases in the rate of poison center exposure calls involving opioids and prevalence of self-reported recent opioid abuse among those entering addiction treatment. However, both of these downward trends began before the REMS was implemented.

In addition, self-reported non-medical use of opioids increased among college students, and the incidence of emergency department visits and hospitalizations for prescription opioid overdose did not change significantly after the REMS came online.

"No study directly evaluates the association between participation in REMS trainings and changes in clinical practice, prescribing behaviors, or patient outcomes," FDA said.

> "The science of evaluating REMS programs ... continues to evolve," FDA REMS Assessment Team Leader Auth said.

Product sponsors said preliminary data from an electronic health records study directly address this issue, although it was not part of the formal assessment plan (*see related story, "Electronic Medical Records May Play Bigger Role In Future REMS Assessments," p. 8*).

## LEARNING FROM PAST ASSESSMENTS

FDA reviewers recommended various approaches to assess the impact of REMS CE going forward, including self control-designed surveys on probability samples, a randomized experiment in which prescribers are assigned to either a training or no training group, and longitudinal studies that track changes in prescribing behavior at the individual provider level before and after REMS-compliant training.

The agency also suggested use of other types of data sources, including national surveys and Centers for Disease Control and Prevention vital statistics data, to monitor overall trends in opioid-related adverse outcomes.

FDA was asked whether some of its current recommendations on study design were considered at the outset of REMS.

"When this REMS was approved back in 2012 it was still fairly early in the development and evaluation of these programs, so I think the science of evaluating REMS programs in particular continues to evolve," REMS Assessment Team Leader Doris Auth said. "At the time what we were focusing on, because this is a continuing education program, is knowledge" and trends in events over time.

She noted that REMS evaluation plans are frequently revised after assessments. "I think it just suffers from somewhat of a lack of experience in doing these things," Auth said of the expectations for the ER/LA opioid REMS assessment.

Yet, even FDA was unsure whether some of its suggested designs for future studies were even feasible.

University of Washington epidemiologist James Floyd questioned whether it was possible to conduct a credible observational study to assess the impact of voluntary education given that the prescribers who take the training may be very different from those who don't.

"This is a question that we've been struggling with as well," said Jana McAninch, a medical officer in the Division of Epidemiology II.

"Evaluating interventions using observational data is really challenging. I think that it's something worth exploring."

### EFFECTIVENESS OF ASSESSMENTS 'LACKING'

Advisory committee members were generally underwhelmed with the ER/LA REMs assessment data.

"Surveys to evaluate knowledge don't really evaluate the REMS," committee chair Almut Winterstein, a University of Florida pharmaceutical outcomes researcher, said in summing up the panel's discussion. "Perhaps they evaluate the short-term quality of the CME program … but not the effect of the CME program on outcomes that really matter that the REMS is focused on."

"The effectiveness of data sources and methodologies has thus far been somewhat lacking," Choudhry said. Surveys should be shorter, generalizable and use better sampling methodology, he said. To address questions about surveillance and drug utilization, he pointed to the emergence of integrated data sources that link across electronic health records, claims data, registries and laboratory data.

"I thought it was kind of disappointing that this was not a carefully thought about evaluation strategy," said University of Michigan biostatistician Trivellore Ragunathan. "I think this needs a careful redrafting of the evaluation plan using measurable outcomes, carefully crafting various designs of experiments and sample surveys, using longitudinal data of detecting the change in behaviors."

"I'm pretty struck with the lack of studies that attempted to address the major goal of the REMS, which was to look at outcomes," Emala said. "In some ways it appears that the lower-hanging fruit was approached with looking at prescriber education and knowledge base." A longitudinal study of prescribers that do and don't take the training, as well as studies that use electronic data sources and administrative data sets to look at outcomes, are imperative, he said.

However, Harvard anesthesiologist Brian Bateman was skeptical that an observational study would be able to capture the impact of a voluntary training program. "This may be a place where an RCT is really necessary to define the effect of the training program," he said.

### RXING APPROPRIATENESS REMAINS A QUESTION

Several panelists said the assessments failed to address the key question of whether the REMS was having an impact on inappropriate prescribing.

"The current REMS program measures level of prescribing, which is very helpful," University of Pennsylvania biostatistician Warren Bilker said. "But it doesn't address at all whether any of the prescribing is appropriate or inappropriate, and I don't think movement can be made without that."

Inappropriate prescribing behavior is "incredibly ripe for analysis of big data," said Ruth Parker, a medical education and health services researcher at Emory University.

However, Paul Stander, chief of medical service at Banner University Medical Center in Phoenix, questioned whether it would ever be possible to measure the impact of the ER/LA opioids REMS.

"I think it's going to be very difficult, if impossible, to segregate out the effect of education versus the myriad other interventions that are going to happen," Stander said.

"It's going to come down to an argument: are we going to look for proof of efficacy to determine whether we keep educating people about this? Or are we going to accept the intuitive belief that … it's hard to see how [education is] harmful unless its unduly burdensome, and that we all believe that if you're prescribing dangerous medicine you ought to learn or be taught how to do it?"



# 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

| SPONSOR | PRODUCT | INDICATION | CODE | APPROVAL DATE |
|---|---|---|---|---|
| **New Drugs** | | | | |
| Biofrontera AG | Ameluz (aminolevulinic acid HCl) | Use of the porphyrin precursor, in combination with photodynamic therapy using *BF-RhodoLED* lamp, for the lesion-directed and field-directed treatment of actinic keratoses of mild-to-moderate severity on the face and scalp | 3 | 5/10/2016 |

| KEY TO ABBREVIATIONS | |
|---|---|
| **Review Classifications** | **NDA Chemical Types** |
| **P:** Priority review<br>**S:** Standard review<br>**O:** Orphan Drug | **1:** New molecular entity (NME); **2:** New active ingredient; **3:** New dosage form;<br>**4:** New Combination; **5:** New formulation or new manufacturer; **6:** New indication;<br>**7:** Drug already marketed without an approved NDA; **8:** OTC (over-the-counter) switch;<br>**9:** New indication submitted as distinct NDA – consolidated with original NDA;<br>**10:** New indication submitted as distinct NDA – not consolidated with original NDA |

# Electronic Medical Records May Play Bigger Role In Future REMS Assessments

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Future assessments of the extended-release/long-acting opioids Risk Evaluation and Mitigation Strategy may look more like the unpublished study that product sponsors unveiled at the May 3-4 FDA advisory committee meeting than the surveys and surveillance data currently being used to measure the program's impact.

During the product sponsors' presentation, Charles Argoff, director of Albany Medical Center's Comprehensive Pain Center, acknowledged that one of the challenges in interpreting the REMS' impact is linking the program's voluntary training with prescriber behavior and patient outcomes.

"A recent retrospective observational study does exactly this," Argoff said, pointing to initial results from a study based on Amazing Charts, an electronic health records system and division of continuing education provider Pri-Med.

The study was not submitted for review by FDA or discussed in either the agency or sponsors' briefing books. However, Argoff said he had permission from Pri-Med to discuss the results.

The study is based on electronic health records data stratified according to whether prescribers had or had not taken REMS-compliant CE. It compared prescribing patterns for ER/LA and immediate-release opioids, as well as patient outcomes such as abuse and dependence, in the time period before REMS training was offered and three years after training implementation, Argoff said.

The study included a cohort of 441 providers who had received REMS-compliant training, and a control cohort of 4,669 providers who had not. Those prescribers who received the education saw an overall decrease of 10% in their ER/LA prescribing, compared to a 4% increase in the untrained group. IR opioid prescribing in both groups increased 3%.

"There were improvements in the outcomes of abuse, dependence and overdose among patients of trained prescribers," Argoff said. "There was a 50% decrease in abuse and dependence diagnoses among these patients compared to a 29% increase in these events among patients cared for by members of the control group. A similar pattern was seen for overdose."

**FDA's Judy Staffa shared some concerns about lack of detailed study findings, including whether the EHRs were linked to death data.**

Photo credit: Kaspars Grinvalds/shutterstock.com

"These prescribing behavior and patient outcome data suggest a positive impact of the ER/LA REMS," Argoff said. "These results provide evidence of the effect within the trained group, particularly compared to the control group who did not improve in any category over time."

## 'IMPRESSIVE,' BUT LOTS OF UNKNOWNS

Advisory committee members and FDA staff were cautious in their approach to the data. Panelist Tobias Gerhard, a drug safety researcher at Rutgers, suggested the data should be taken with a grain of salt.

Gerhard noted the number of overdoses was in the single digits, and prescribers who volunteered for the CE program may not be comparable to those who did not. In addition, the use of ICD codes in electronic health records may not be the most sensitive instrument for measuring abuse and dependence, he said.

"I don't think we know enough from this study to take it really into consideration," Gerhard said. "These numbers as presented … look very impressive, but I don't think at this point there is enough there to allow us to really take those as a true finding."

Judy Staffa, acting associate director for public health initiatives in FDA's Office of Surveillance and Epidemiology, shared some of Gerhard's concerns on the lack of detailed study findings. For example, she questioned whether the electronic health records were linked to death data. "What we've seen in the past is if you don't include people who died, it can often distort what you're seeing because you're focusing" only on those patients who are alive, she said.

Argoff said that although death outcomes are not captured in the database, it might be possible to link to the National Death Index. Future analyses of the Pri-Med study for publi-

cation will include comparison of patient and provider characteristics, statistical significance testing, and adjustments for covariates with propensity score matching, he said.

Paul Coplan, head of medical affairs strategic research at **Purdue Pharma LP** and chairman of the REMS Products Companies' Metrics Subteam, said that while the Pri-Med study was not part of the assessment plan, "it gives a sense of the type of study you could do and the kind of measures you could get at."

This sort of study, where CE provider data are linked with electronic health records data on prescribing and patient outcomes, was not envisioned at the time the REMS assessment plan was under development, he said.

Coplan suggested this type of approach also is a work-around to restrictions that product sponsors face in learning who has taken REMS-compliant CE training (*"Opioid Continuing Education Rules Hamper REMS Assessments" — "The Pink Sheet" DAILY, May 3, 2016*).

Although they had not reviewed the Pri-Med data, FDA officials acknowledged the study could serve as a model for future assessments.

"Certainly we agree now that, especially as we've seen from what Dr. Argoff presented earlier, this type of data is potentially doable and we look forward to trying to do some sort of study and get this information moving forward," REMS Assessment Team Leader Doris Auth said.

Panelists also saw a role for electronic health records-based studies in future assessments, especially since they found the current tools lacking (*see related story, "REMS Assessment Challenges Shine Through In Opioids Review," p. 5*).

# EMA's PRIME: Helpful But Not A Panacea

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Regulators believe the various benefits and incentives that will be on offer under PRIME, the European Medicines Agency's new priority medicines scheme, will be helpful to drug developers deemed eligible for entry but the program should not be regarded as a panacea.

"Being out of PRIME is not the worst thing in the world," according to Robert Hemmings, the UK representative who chairs the EMA's scientific advice working party, the group responsible for reviewing applications for entry into the scheme. "No one is positioning PRIME as a sort of panacea," he said in a presentation to the joint UK BioIndustry Association (BIA)/Medicines and Healthcare products Regulatory Agency (MHRA) conference on Accelerated Development and Access to Innovative Medicines for Patients on May 4 in London.

Outside of PRIME, Hemmings said, the EMA will try "just as hard" when it gives companies scientific advice "to give you good advice about the development plan." Also, he said, companies using the European centralized procedure still have the possibility to request an accelerated assessment (the route PRIME-designated products are expected to take), and they can use other EU processes or tools aimed at fostering early access such as conditional marketing authorization or marketing authorization under exceptional circumstances, "if that's appropriate."

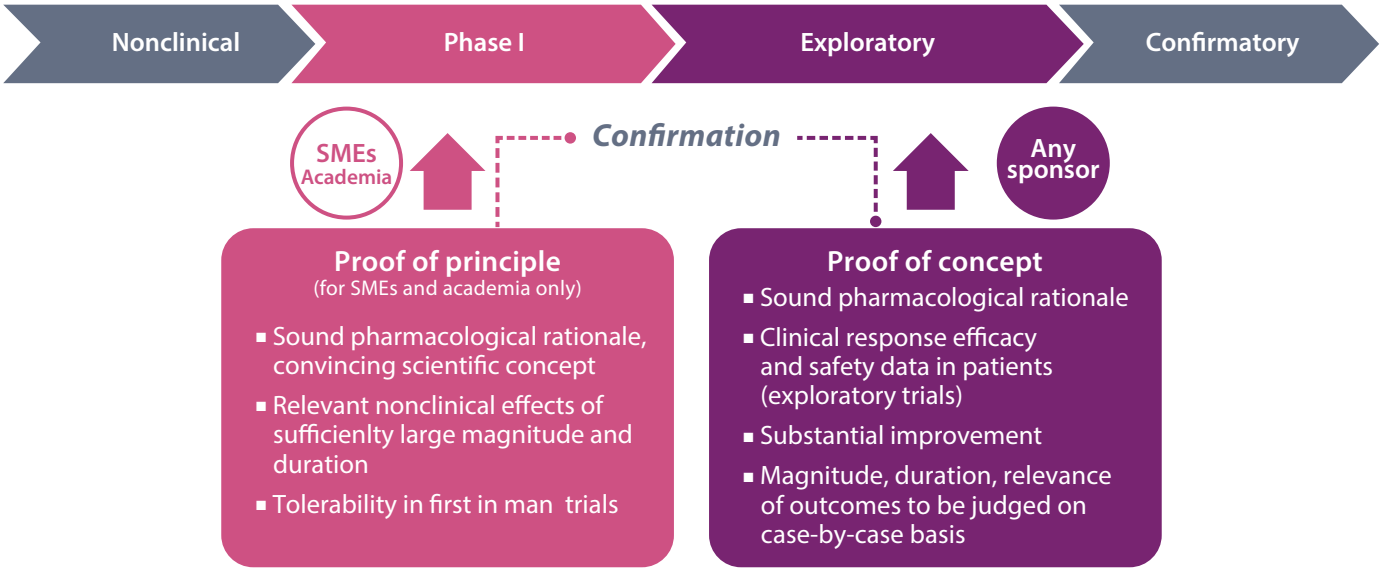
PRIME centers on providing early and enhanced scientific and regulatory support to developers of potentially transformative medicines to optimize the generation of robust data and enable accelerated assessment. The EMA hopes it will be of particular help to smaller developers and applicants from the academic sector who for one reason or another may struggle to get their promising products to a stage where they can be submitted for approval (*"PRIME Time: Smaller Companies In Focus As EMA Launches Priority Medicines Scheme" — "The Pink Sheet" DAILY, March 7, 2016*). A total of 26 applications for entry were received within two months of the scheme's March 7 launch. The fate of the first 18 should be known by the end of May (*"EMA's New PRIME Scheme Gets 18 Applications In First Month" — "The Pink Sheet" DAILY, April 7, 2016*).

Some companies may not be interested in applying for entry into PRIME; others will apply but will be rejected. Critically, products eligible for PRIME should demonstrate the potential to address to a significant extent an unmet medical need. Equally – indeed perhaps even more – critically, products can only apply for entry into PRIME at very specific points in their development. SMEs (small and medium-sized enterprises) and applicants from academia have the choice of applying either at the proof-of-principle stage (i.e., prior to Phase II/exploratory clinical studies) or at the later proof-of-concept stage (i.e., prior to Phase III/confirmatory clinical studies). All other applicants can only apply at the later stage.

Jordi Llinares Garcia, the EMA official who heads up the department responsible for developing PRIME, reiterated during the conference that products are not eligible if they are at a very early stage of development (i.e., before even proof-of-principle), are already authorized (and where the applicant is looking for approval of another indication, for example), or are already at the pre-submission stage. A slide from Llinares's presentation shows the entry points for PRIME eligibility and the required evidence (*see graphic, p. 10*).

Llinares and Hemmings highlighted some of the key features of PRIME, including the early appointment of a rapporteur from the EMA's Committee for Medicinal Products for Human Use and the so-called "kick-off meeting" involving the sponsor and a multidisciplinary group of experts from relevant EMA scientific committees

## Entry Points PRIME Eligibility And Required Evidence




*Source: EMA*

and working parties.

The early appointment of a CHMP rapporteur will allow sponsors to benefit from "enhanced dialogue with someone who knows the inside of the regulatory system and signposts them towards topics of timing for centralized scientific advice and can engage with them on issues that don't perhaps need a central view from the CHMP about the dossier," Hemmings told the meeting. The rapporteur will be able to advise on the timing of submission – looking at "this idea of when might the benefits outweigh the risks" – and start discussions about post-authorization activities, for example. More broadly, it will help sponsors "generally get prepared for this exercise of accelerated assessment" and make that "as smooth and as optimal" as possible.

The kick-off meeting will help sponsors deal with "one of the challenges of the regulatory system in Europe," that is, potentially having to face up to five scientific committees for human medicines at the EMA. "You may be developing an advanced therapy in a rare disease that includes children and then you've got five committees to negotiate," Hemmings said. The kick-off meeting is aimed at getting "everyone on the same page" for the development program and that "single stream of discussion can be continued through the scientific advice once those bridges are built."

The EMA has high hopes for PRIME. Llinares concluded his presentation by saying that the scheme would "hopefully allow patients to benefit from therapies that may change their lives significantly."

*[Editor's note: This article is also published in Scrip Regulatory Affairs. The Pink Sheet brings selected complementary coverage from sister publications to our readers.]*



# FDA's ANDA Approvals

| SPONSOR | ACTIVE INGREDIENT | DOSAGE; FORMULATION | APPROVAL DATE |
|---|---|---|---|
| Aurobindo | Fenofibrate | 48 mg and 145 mg; tablet | 5/5/2016 |
| Indicus | Desipramine HCl | 10 mg, 25 mg, 50 mg, 75 mg, 100 mg and 150 mg; tablet | 5/5/2016 |
| Watson (now Actavis) | Dienogest/estradiol valerate | N/A/3 mg, 2 mg/2 mg, 3 mg/2 mg, NA/1 mg; tablet | 5/6/2016 |
| Nostrum Labs | Dapsone | 25 mg and 100 mg; tablet | 5/6/2016 |
| Par | Sodium phenylbutyrate sodium | 500 mg; tablet | 5/6/2016 |
| **TENTATIVE APPROVALS** | | | |
| Amneal | Levoleucovorin | 50 mg; injection | 5/9/2016 |

# Many PRIME Applicants Are Missing Pediatric Investigation Plans

**MAUREEN KENNY** maureen.kenny@informa.com

Two thirds of the applications submitted for entry into the European Medicines Agency's new PRIME (priority medicines) scheme in the first month after its launch were missing a pediatric investigation plan or a PIP waiver.

For 12 of the 18 applications, the EMA would have expected a PIP or waiver to be under discussion with the agency, but "they were not there," said Dr Jordi Llinares García, the EMA official who heads the department responsible for the scheme. This was the only negative point – Llinares described it as "a warning, a word of caution" – in an otherwise upbeat presentation he gave on PRIME at the joint BioIndustry Association (BIA)/Medicines and Healthcare products Regulatory Agency (MHRA) Conference on Accelerated Development and Access to Innovative Medicines For Patients.

> Aside from the PIP issue, all of the first 18 applications were "in scope" and of a quality that meant the assessments could be done without the EMA having to go back to any of the applicants.

With some of the applications for PRIME, clinical trials were already taking place in children without there having been any discussion with the EMA's pediatric committee, the PDCO. "That is not an ideal situation … that is something we want really to avoid," Llinares said in a conversation at the conference sidelines.

The timing of PIP submissions has long been controversial. Companies continue to struggle to submit them on time as they believe they are required too early. PIPs are mandatory for all new medicines evaluated through the EU centralized procedure unless a waiver or deferral is granted. The Paediatric Regulation (No 1901/2006) says applications for PIPs should be submitted not later than upon completion of pharmacokinetic studies in humans. The EMA interprets this to mean at the end of Phase I clinical trials in adults, a point Llinares confirmed .

Most of the 18 applications received in the first month after PRIME's March 7 launch relate to products that are at the later, proof-of-concept stage (*"EMA's PRIME: Helpful But Not A Panacea" — "The Pink Sheet," May 16, 2016*). (Another eight applications were received later.)

The implication is that all products applying to enter PRIME at the proof-of-concept stage should have a PIP or waiver in place or at least under discussion with the PDCO. Asked about this point, EMA said that while "in standard developments, human PK studies are often conducted prior to generation of proof of concept data … this has to be considered on a case-by-case basis, depending on the type of product and studies conducted."

Llinares suggested that the number of initial applications submitted at proof-of-concept stage could be down to timing. Companies were perhaps waiting for the scheme to launch and "I guess this will change in the future and more people will come at an early stage."

The lack of a PIP or waiver does not prejudice against the application, the UK BioIndustry Association said. BIA points out that the PRIME guidance for applicants specifically states that the kick-off meeting that will take place once a product has been granted eligibility for PRIME provides the opportunity for early dialogue between applicants and the PDCO regarding the strategy for the PIP in advance of a PIP application.

EMA for its part says that the kick-off meeting will be an opportunity to discuss development plans and upcoming submissions with relevant EMA committees. The agency says that the intent of the statement in the guidance that the BIA cites "was to clarify that discussions that may otherwise be held during an early pediatric interaction meeting might be held in the context of the kick-off meeting."

EMA says it will remind applicants to PRIME of the need to comply with pediatric requirements with respect to submission of a PIP. It will address this on a case-by-case basis, depending on the stage of development of the concerned product. The points made by Llinares during his presentation, it said, were to "highlight the importance of considering pediatric requirements timely in development programs." The agency will "ensure awareness is raised amongst sponsors of such requirements."

Aside from the PIP issue, all of the first 18 applications were "in scope" and of a quality that meant the assessments could be done without the EMA having to go back to any of the applicants. Either you are very good or our templates are very good or both," joked Llinares.

"Almost all therapeutic areas" were covered in the first round and "that is really, really good," he reported. Two submissions were for advanced therapy medicinal products, which are items such as engineered tissue products and cell and gene therapy.

The fate of the first batch of applications will be made known after the May 23-26 meeting of the EMA's scientific committee, the CHMP, which is responsible for the adoption of recommendations made on PRIME eligibility by the EMA's scientific advice working party (SAWP). At that time, EMA will release the name of the active substance or INN of the products accepted onto the scheme, Llinares said.

The EMA official revealed that eleven of the 18 applications were from small and medium-enterprises, a key target of the new program (*"PRIME Time: Smaller Companies In Focus As EMA Launches Priority Medicines Scheme" — "The Pink Sheet" DAILY, March 7, 2016*)

Llinares noted that the EMA and FDA are planning to share information on PRIME and the US "breakthrough" designation program (*"EMA, FDA Get Together On Drugs Eligible For PRIME And Breakthrough Designation" — "The Pink Sheet," May 2, 2016*). In addition, there will be a workshop on PRIME once it has been in place for a year to share experiences and to see how we can "further improve" the scheme.

# Medicare Payment Demo Would Put Often-Prescribed Cancer Drugs 'Underwater'

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Nearly 50 of the most frequently-prescribed oncology or treatment-related drugs would be 'underwater' – or reimbursed at less than acquisition cost – under the payment rate in the Medicare demonstration project recently proposed by the Centers for Medicare and Medicaid Services, according to the Community Oncology Alliance.

In May 9 comments to CMS, the oncology provider organization takes issue with the agency's claim that the proposed payment approach would help ensure that prescribing decisions are based on the value of treatments and not the profits that could be generated through the use of expensive drugs.

CMS proposes testing an alternative to the current average sales price (ASP) plus 6% reimbursement formula for Medicare Part B drugs, instead paying at ASP plus 2.5% and a flat $16.80 fee, thus reducing the amount of reimbursement that is based on a drug's price (*"CMS Unveils Bold Approach To Managing Medicare Part B Drug Costs" — "The Pink Sheet" DAILY, March 8, 2016*).

The proposal is designed to be "budget neutral," meaning CMS expects its overall Part B payments would remain the same, but payments for some very expensive drugs would be reduced and reimbursement for low-cost drugs would increase. The demonstration is expected to particularly impact oncology, ophthalmology and rheumatology practices. Medicare spending on Part B drugs totaled $22bn in 2015.

However, the Community Oncology Alliance (COA) argues, "there are very few situations in cancer treatment when alternative drugs exist that are differentiated in price/cost. So the Part B proposal, while ostensibly focused on controlling costs, is valuing less-important drugs … and not the most important, highest-value cancer treatment drugs that are standard-of-care therapy."

COA says it modeled the impact of the demonstration in collaboration with practicing medical oncologists and practice administrators and found that 47 drugs would be reimbursed at below acquisition cost under the alternative payment approach (*see chart*). Reimbursement for nearly half of those drugs will be reduced by well over $100 per dose under the demo, according to COA's figures.

Two treatments, **Valeant Pharmaceuticals International Inc.** *Provenge* (sipuleucel-T) and **Bristol-Myers Squibb Co.**'s *Yervoy* (ipilimumab), will see reductions of more than $1,000 per dose.

The analysis assumes that under the federal budget sequester, the actual payment amount paid in the test would be only ASP plus .86% and the flat fee would be reduced to $16.53. In its model, COA compares that payment rate to the current effective rate under the sequester, which is ASP plus 4.3%.

Community oncology practices have been among the most vocal critics of the Part B demonstration, driven by concerns over financial repercussions of reduced reimbursement. Provider and patient-oriented arguments against the demonstration will be aired at a House subcommittee hearing May 17 (*"Provider Opposition To Medicare Part B Demo Will Get House Hearing" — "The Pink Sheet" DAILY, May 11, 2016*).

Almost 70% of cancer patients are treated in an office-based or community oncology setting, according to COA, and the remaining patients are treated in hospital outpatient facilities.

## HOSPITALS SEEK EXEMPTION, PROPOSE ALTERNATIVES

In separate May 9 comments to CMS, the American Hospital Association also challenged the demonstration project. "There is no convincing evidence that physicians who practice in hospital outpatient department (HOPD) settings consider profitability over clinical effectiveness when deciding which drugs to prescribe or order," AHA argues.

Furthermore, "hospitals have little control over which drugs physicians order in HOPD settings. Yet this model would hold them accountable for these decisions – to the extent that they would bear 60% of the aggregate payment reduction."

Therefore, "it is clear that hospitals are inappropriate for inclusion in this model," the group maintains.

However, AHA says if CMS continues to include hospitals in the experiment, "we strongly recommend that the model be implemented on a much smaller scale by excluding cancer drugs and narrowing the number of geographic areas that are affected."

Under the current plan, participation in the model would be mandatory for all providers and suppliers of Part B drugs located in selected geographic areas. Physicians and hospitals in half the nation would receive Part B payments at the alternative rate plus the flat fee and the other half would continue to be paid under the ASP plus 6% formula.

AHA also recommends that CMS "tailor" the experiment to select physician specialties or conditions treated by multiple drugs that are substitutable and vary considerably in price, or to clinically complex conditions with "several" therapeutically equivalent treatment options.

AHA suggests a number of alternative approaches to the proposed ASP plus 2.5% and $16.80 flat fee. For example, drugs with an ASP of less than $100 could get ASP plus 2.5% and a $5 flat fee, while drugs costing more than $100 would receive ASP plus 2.5% and a $31.97 flat fee, the group says.

Under another option, drugs costing more than $100 but less than $480 would get ASP plus 2.5% and a $16.80 fee and drugs with an ASP of greater than $480 would be paid at ASP plus 2.5% and a flat fee of $47.98.

# Oncology Drugs Underwater In Part B Payment Model

The Community Oncology Alliance gave CMS a list of 47 oncology treatment or supportive care drugs that it says would be "underwater" – reimbursed at less than acquisition cost – under the Medicare demo based on "actual practice cost." COA says the list of underwater drugs would be "far longer" if the costs of procurement, storage, preparation and waste disposal were considered as well.

| DRUG | SPONSOR | APPROVED INDICATIONS | CURRENT PAYMENT PER DOSE: ASP + 4.3% | DEMO PAYMENT PER DOSE: ASP +.86%, $16.53 | DIFFERENCE |
|---|---|---|---|---|---|
| Actemra (tocilizumab) | Roche | rheumatoid arthritis | $2,167.60 | $2,112.56 | $55.04 |
| Adcetris (brentuximab vedotin) | Seattle Genetics | lymphomas | $16,369.56 | $15,845.59 | $523.97 |
| Alimta (pemetrexed) | Eli Lilly | non-small cell lung cancer | $5,492.37 | $5,237.55 | $164.82 |
| Aranesp (darbepoetin alfa) | Amgen | anemia | $871.18 | $858.95 | $12.23 |
| Avastin (bevacizumab) | Roche | colorectal cancer, | $1,298.74 | $1,272.39 | $26.35 |
| Cyramza (ramicirumab) | Eli Lilly | gastric, non-small cell lung and colorectal cancers | $8,192.04 | $7,938.08 | $253.96 |
| Dacogen (decitabine) | Eisai/Otsuka | myelodysplastic syndromes | $1,099.12 | $1,079.35 | $19.76 |
| Elitek (rasburicase) | Sanofi | plasma uric acid management | $5.047.25 | $4,897.13 | $150.12 |
| Erbitux (cetuximab) | Eli Lilly | colorectal, head and neck cancers | $2,888.84 | $2,809.99 | $76.86 |
| Faslodex (fulvestrant) | AstraZeneca | breast cancer | $1,776.38 | $1,734.25 | $42.12 |
| Feraheme (ferumoxytol) | AMAG Pharmaceuticals | anemia | $420.11 | $422.77 | $2.66 |
| Folotyn (pralatrexate) | Spectrum Pharmaceuticals | T-cell lymphoma | $9,506.06 | $9,208.71 | $297.35 |
| Fusilev (levoleucovorin) | Spectrum Pharmaceuticals | rescue after chemo in bone cancer | $916.27 | $902.55 | $13.72 |
| Gammagard (immune globulin) | Baxalta | replacement therapy | $2,811.51 | $2,735.21 | $76.30 |
| Gammaked (immune globulin) | Kedrion Biopharma | primary immune deficiency | $3,329.27 | $3,253.87 | $93.40 |
| Gazyva (obinutuzumab) | Roche | lymphoma, chronic lymphocytic leukemia | $3,296.62 | $3,204.30 | $92.32 |
| Halaven (eribulin) | Eisai | breast cancer, liposarcoma | $2,505.37 | $2,439.17 | $66.19 |
| Herceptin (trastuzumab) | Roche | breast, gastric cancers | $3,211.91 | $3,122.30 | $89.52 |
| Injectafer (ferric carboxymaltose) | American Regent | anemia | $812.49 | $802.20 | $10.30 |
| Istodax (romidepsin) | Celgene | T-cell lymphoma | $7,893.37 | $7,649.27 | $244.10 |
| Ixempra (ixabepilone) | Bristol-Myers Squibb | breast cancer | $4,018.29 | $3,902.14 | $116.15 |
| Jevtana (cabazitaxel) | Sanofi | prostate cancer | $8,516.10 | $8,251.44 | $264.66 |

| DRUG | SPONSOR | APPROVED INDICATIONS | CURRENT PAYMENT PER DOSE: ASP + 4.3% | DEMO PAYMENT PER DOSE: ASP +.86%, $16.53 | DIFFERENCE |
|---|---|---|---|---|---|
| Kadcyla (ado trastuzumab emtansine) | Roche | breast cancer | $7,563.74 | $7,330.53 | $233.21 |
| Keytruda (pembrolizumab) | Merck | melanoma, non-small cell lung cancer | $8,276.80 | $8,020.04 | $256.76 |
| Kyprolis (carfilzomib) | Amgen | multiple myeloma | $1,853.78 | $1,809.10 | $44.68 |
| Lupron (leuprolide) | AbbVie | prostate cancer | $1,930.84 | $1,883.62 | $47.22 |
| Neulasta (pegfilgrastim) | Amgen | neutropenia | $3,836.03 | $3,725.90 | $110.13 |
| Nplate (romiplostim) | Amgen | platelet producer | $221.74 | $2,164.92 | $56.83 |
| Octagam (immune globulin) | Octapharma | primary humoral immunodeficiency | $3,077.34 | $2,992.26 | $85.08 |
| Opdivo (nivolumab) | Bristol-Myers Squibb | melanoma, non-small cell lung and renal cell carcinoma | $5,952.00 | $5,772.00 | $180.00 |
| Perjeta (pertuzumab) | Roche | breast cancer | $6,471.96 | $6,274.80 | $191.17 |
| Privigen (immune globulin) | CSL Behring | primary humoral deficiency, immune thrombocytopenic purpura | $2,924.85 | $2,844.81 | $80.04 |
| Provenge (sipuleucel-T) | Valeant Pharmaceuticals | prostate cancer | $37,733.75 | $36,504.35 | $1,229.39 |
| Remicade (infliximab) | Janssen | Inflammatory disease | $3,837.88 | $3,727.69 | $110.19 |
| Rituxan (rituximab) | Roche | non-Hodgkin lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis | $5,833.30 | $5,657.22 | $176.08 |
| Sandostatin (octreotide) | Novartis | acromegaly, carcinoid syndrome | $152.40 | $163.90 | $11.50 |
| Somatuline depot (lanreotide) | Ipsen | acromegaly, carcinoid syndrome | $5,005.23 | $856.50 | $148.74 |
| Torisel (tesirolimus) | Pfizer | renal cell carcinoma | $1,555.39 | $1,520.56 | $34.83 |
| Treanda (bendamustine) | Teva | chronic lymphocytic leukemia, non-Hodgkin lymphoma | $4,051.42 | $3,934.18 | $117.24 |
| Trisenox (arsenic trioxide) | Teva | promyelocytic leukemia | $932.66 | $918.39 | $14.26 |
| Tysabri (natalizumab) | Biogen | multiple sclerosis | $5,029.40 | $4,879.86 | $149.53 |
| Vectibix (panitumumab) | Amgen | colorectal cancer | $4,729.01 | $4,589.40 | $139.63 |
| Velcade (bortezomib) | Takeda | multiple myeloma, mantle cell lymphoma | $1,515.60 | $1,482.09 | $33.51 |
| Vidaza (azacitidine) | Celgene | myelodysplastic syndrome, myeloid leukemia | $510.61 | $510.28 | $0.33 |
| Xgeva (denosumab) | Amgen | bone metastases | $1,310.23 | $1,283.50 | $26.73 |
| Yervoy (ipilimumab) | Bristol-Myers Squibb | melanoma | $35,470.35 | $34,315.60 | $1,154.66 |
| Zaltrap (ziv-aflibercept) | Sanofi | colorectal cancer | $2,587.26 | $2,518.36 | $68.90 |

# A New Type of Investor Relations for Biopharma

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The biopharma industry leadership is getting an earful from some powerful people about their pricing practices. No, we are not talking about Hillary Clinton, Bernie Sanders, Donald Trump or any of the members of Congress weighing in on drug costs.

We are talking about some of the largest investors in biopharma.

According to Bloomberg, a group of leading investors met with industry leaders (including key executives in the BIO and PhRMA trade associations) in Boston last month "to urge to do a better job in defending their industry and take control of the conversation before lawmakers try to regulate prices."

Now, it is not like the industry's Washington advocates have been ignoring the issue. But that isn't really the important message from the meeting. Rather, it is the latest sign that the politicians attacking drug pricing have found a lever that may actually be effective to drive change: the declining stock price.

It has been interesting to watch the disconnect between the substance of the Washington threat to drug pricing and investor reactions. When Henry Waxman wrote a letter demanding justifications for **Gilead Sciences Inc.**'s pricing of *Sovaldi* in 2014, it had no chance of leading to hearings, much less legislation – but it sure spooked investors (*"Washington Threatens; Wall Street Reacts" — The RPM Report, April 2014*).

When Hillary Clinton tweeted her "outrage" of **Turing Pharmaceuticals AG**'s price increases, most pundits in Washington still assumed there was a strong chance that the next President would be a Bush or a Rubio – but investors reacted as if Clinton was already in office with a Democratic Congress ready to enact her plan in the first 100 days (*"When Empty Threats Work: "Price Negotiation" In White House Budget Spooks Wall Street" — The RPM Report, February 2015*).

But perhaps the best example of the attempt to apply political pressure via activist investors has come from the Senate Aging Committee. In its two recent hearings on drug price increases (focusing primarily on Turing and **Valeant Pharmaceuticals International Inc.**), the committee put an unusual twist on the witness list. The basic format was typical: a panel of patients and providers to testify about the harms caused by extreme price increases followed by executives from the companies to face grilling about their practices.

At two recent Senate hearings on drug price increases, there was an extra witness at the table: a large investor.

But in both hearings, there was an extra witness at the table: a large investor. During the first hearing, the investor was Dan Wichman from Broadfin Capital, who helped fund Martin Shkreli's first company (Retrophin) but did not invest in Turing. During the second hearing, Valeant investor William Ackman (Pershing Square) was at the witness table – and in fact was perhaps the most effective in convincing the panel that Valeant is indeed reforming its practices(*"Congress Already Impacting Industry Drug Pricing Abuses, Valeant Says" — "The Pink Sheet" DAILY, April 27, 2016*).

The theme was set up in questioning by Sen. Thom Tillis (R-NC), who questioned Valeant about the relative size of its sales from "re-priced" drugs versus its lost market capitalization in the context of the criticism. Ackman stressed that the market cap collapse had indeed catalyzed change at the company and delivered a message across the industry that the practice of acquiring older products to "re-price" them must end. By the end of the hearing, Ackman even seemed to win over skeptics of Valeant's sincerity by arguing that his new role on Valeant's board is in line with Pershing's posture as an activist, hands-on investor, in contrast to its more "passive" role with Valeant previously.

Ackman's message resonated all the more because of the pending management change at Valeant, with outgoing CEO Michael Pearson offering a very public *mea culpa* as one of his last actions before stepping down.

Whatever else follows, the Turing/Valeant story will reinforce the message that jawboning remains an effective strategy for combating prescription drug prices at the federal level in the US. That is not a new insight – but each new case lays out paths for future investigators to explore.

There is no government mechanism to set drug prices in the US, and (barring a Bernie Sanders single payor landslide) there isn't likely to be one any time soon. But by putting pressure on biopharma investors, politicians may have found a way to rein in or curb perceived abuses without needing to enact new policies.

*[Editor's note: This story was first published in The RPM Report. The Pink Sheet brings selected complementary coverage from sister publications to our subscribers.]*

# Incyte's Oncology Strategy: Putting Its Eggs In Many Mechanistic Baskets

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The financial springboard supplied by the successful JAK inhibitor *Jakafi* is allowing **Incyte Corp.** to tackle many new mechanisms all at once, including a second-generation PI3 kinase inhibitor and some of the hottest targets in immuno-oncology today – OX40 and GITR agonists – and rebound from some R&D disappointments.

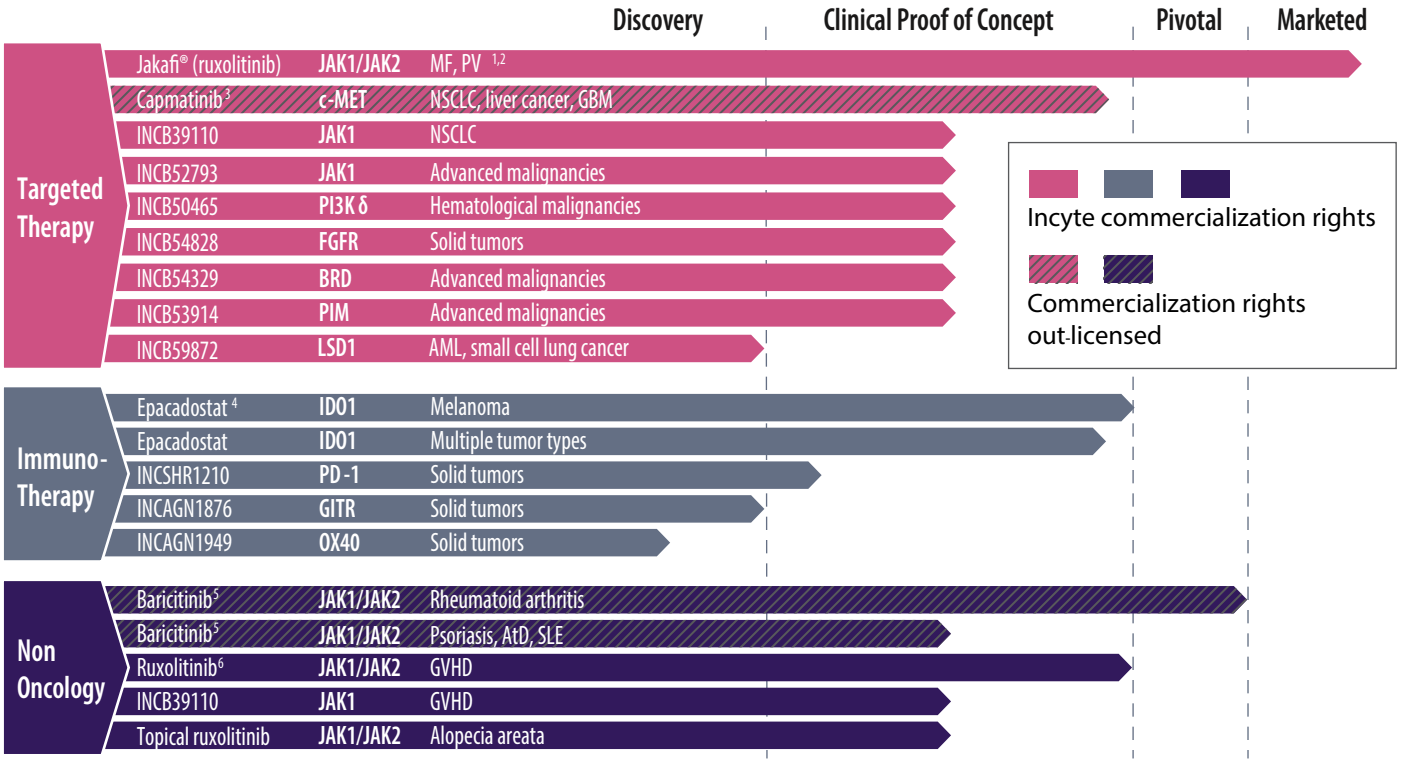
The company showcased its full pipeline at the American Association for Cancer Research annual meeting in April and is planning on data releases in the second half of the year, perhaps at the European Society for Medical Oncology meeting in October, though during a May 9 earnings call the company said that it's too early to say what might be included in the program.

Incyte's pipeline has been undergoing rapid change, execs noted during an investor presentation at AACR, with seven new mechanisms added over the last 24 months. It now has 14 candidates in development, including large and small molecules, spanning 11 different mechanisms.

Whereas the pipeline in the past was heavily weighted toward targeted therapy – a number of programs were related to the JAK family of products – it has been evolving over the last 12 months to give the company a greater stake in immunotherapy, CEO Herve Hoppenot pointed out during a presentation at the AACR meeting.

The IDO1 inhibitor epacadostat was the only immuno-oncology drug in development as of April 2015, but the portfolio now includes three other kinds of immuno-on-

## Incyte Pipeline: April 2016




1. Patients with intermediate or high-risk myelofibrosis
2. Patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea
3. Worldwide rights to capmatinib licensed to Novartis, GBM = Glioblastoma multiforme
4. Phase 3 trial expected to begin in H1 2016
5. Worldwide rights to baricitinib licensed to Lilly, AtD = Atopic dermatitis, SLE = Systemic lupus erythematosus
6. Registration trial expected to begin in H2 2016

Incyte notes that it has taken steps to balance and diversify its development portfolio, including large and small molecules.

*Source: Incyte investor presentation, April 17*

cology candidates: INCSHR1210, a PD-1 inhibitor licensed from **Jiangsu Hengrui Medicine Co. Ltd.**; and two preclinical molecules developed with partner **Agenus Inc.** INCAGN1876, a GITR agonist and INCAGN1949, an OX40 agonist (*"Incyte Will Tap Agenus Platform To Move Into Checkpoint Modulator Space" — "The Pink Sheet" DAILY, Jan. 9, 2015*). (*See chart.*)

Incyte's *Jakafi* (ruxolitinib) has proven very successful with its initial approvals for myelofibrosis and polycythemia vera. But the company has had some setbacks with further development in solid tumors, notably the recent failure in pancreatic cancer and the termination of solid tumor trials investigating the link between inflammation and cancer (*"Incyte Ends Jakafi Pancreatic Cancer Trials, But Has More Irons In The Fire" — "The Pink Sheet" DAILY, Feb. 11, 2016*). Still, driven by Jakafi, the company's total revenue rose from $511m in 2014 to $754m in 2015. A pivotal trial of Jakafi in graft-versus-host disease (GVHD) is set to start in the second half.

In its May 9 earnings release, the company reported sales for Jakafi of $183m, up by 59% from the same time last year and increased its full year net revenue guidance from $800m to $815m. The same day, Incyte announced that it was acquiring the European operations of **Ariad Pharmaceuticals Inc.,** including 125 employees, and regional rights to the BCR-ABL inhibitor *Iclusig* (ponatinib), which is approved for chronic myeloid leukemia and Philadelphia-positive acute lymphoblastic leukemia. The deal includes a $140m upfront payment. The company said that the deal will help maximize the launch success of its own products in Europe. In a May 9 note, Jefferies analyst Brian Abrahams pointed out that Iclusig sales could help offset expenses related to developing wholly-owned assets until new pipeline drugs are approved.

In addition, the rheumatoid arthritis drug baricitinib was recently filed by partner **Eli Lilly & Co.** and the launch will bring additional royalties to Incyte in the future (*"Keeping Track: Lilly Files Baricitinib; FDA Approves New Uses For Novartis' Cosentyx" — "The Pink Sheet," Jan. 25, 2016*).

For a company of its size, Incyte is in the unique position where it doesn't need to make trade-offs in its pipeline, rather it is able to move everything forward together in parallel, guided by the science, data and belief in a path forward, Chief Science Officer Reid Huber said in an interview.

To date, epacadostat has become the center of attention in Incyte's pipeline. Promising mid-stage data combining epacadostat with Merck's PD-1 inhibitor *Keytruda* (pembrolizumab) were presented in November at the Society for Melanoma Research annual meeting and a Phase III study of the combination in this indication is set to start in the second half (*"New PD-1 Immunotherapy Combinations Push The Envelope In Melanoma" — "The Pink Sheet," Nov. 30, 2015*).

Epacadostat is in development across 13 tumor histologies in over 900 patients. The development program includes combination studies with the four major sponsors of PD-1/L1 drugs: Bristol, Merck, Roche and AstraZeneca. Data from Phase II expansion cohorts will be released in the second half. The company also is looking forward to the start of enrollment of the Phase III ECHO-301 study of epacadostat with Merck's PD-1 inhibitor *Keytruda* (pembrolizumab) for first-line melanoma in the "coming weeks." Initial data should be released in 2018.

The company will have data from Phase I/II studies for epacadostat in 2016 but declined to comment during its earnings call more specifically in terms of which studies and in what tumor types.

It's a very broad program but Huber notes that the company is "clearly able to fund that effort and move aggressively into that space without sacrificing in any way what we are doing with other parts of the early development pipeline."

Leerink Swann analyst Michael Schmidt commented in an April 18 note that while most investors are focused on epacadostat, which is the main value driver in the near term, the "company's early stage pipeline provides several shots on goal and offers diversification long term."

## INCYTE'S KEY DEVELOPMENT GOALS

- Combination of agents that target T-cells directly with agents that modulate the tumor microenvironment may provide optimal anti-tumor immunity.
- Epigenetic mechanisms such as BRD inhibition provide an alternative intervention point for regulating anti-tumor immunity by modulating the tumor microenvironment.

## BEATING ZYDELIG'S LIVER RAP

Of Incyte's 10 presentations at the AACR meeting, one featured clinical data – a Phase I dose escalation trial of INCB50465, the company's once-daily second-generation PI3 kinase-delta inhibitor, in a range of B-cell malignancies, including follicular lymphoma, diffuse large B-cell lymphoma and chronic lymphocytic leukemia.

The PI3 kinase class has been damaged by experience with **Gilead Sciences Inc.**'s *Zydelig* (idelalisib), which was approved by FDA in mid-2014 with a boxed warning for severe liver toxicity and has had low sales since (*"The Safety Factor" — "The Pink Sheet," Oct. 20, 2014*). More recently, new studies of Zydelig were put on clinical hold due to adverse events related to infections when used as part of combinations with commonly used drugs for B-cell malignancies (*"Zydelig Takes Major Hit, But Not A Big Blow For Gilead" — "The Pink Sheet" DAILY, March 14, 2016*).

As newer members of the class, Incyte's INCB50465 and **TG Therapeutics Inc.**'s TG-1202, which is also given once daily, have a structure that has been modified in order to significantly minimize hepatotoxicity side effects.

Furthermore, there are differences in potency. Chief Medical Officer Steven Stein noted that based on published data,

INCB50465 is 10 times more potent than the first-generation compounds, both of which are given twice daily – Zydelig and **Infinity Pharmaceuticals Inc.**'s duvelisib – and 100-fold more potent than TG's TG-1202.

The response rate in Incyte's just-reported Phase I study was 60%, including three complete responses, and the disease control rate was 73%

The candidate was well-tolerated over the study period of almost 13 weeks, with no dose-limiting toxicities or need for dose reduction. The rate of Grade 3 and greater adverse events was about 40%, including two cases of anemia, one of bacteremia and one Escherichia infection.

Liver enzyme changes were reported, but did not exceed Grade 1. The company acknowledges that follow-up was relatively short, but on the other hand this effect is usually seen fairly quickly.

The risk for infection seen with Zydelig is likely to be related to the mechanism of action, but it may be possible to treat patients prophylactically to minimize these effects, Huber commented.

"It's something that gives us some pause, we certainly have to be cautious as we move forward," he told "The Pink Sheet."

On top of the adverse event baggage, PI3 kinase inhibitors face a competitive threat from **Johnson & Johnson/AbbVie Inc.**'s successful BTK inhibitor *Imbruvica* (ibrutinib), which also is positioned for a range of B-cell malignancies and has demonstrated a fairly benign safety profile.

The targets are very different though, and there may be potential to combine INCB50465 with BTK inhibitors.

"Any decisions we make necessarily have to take into account where that agent is being used and how it is changing the standard of care," Huber said.

Incyte is planning to start multiple expansion cohorts evaluating INCB50465 as a monotherapy and as part of combination therapy in B-cell malignancies.

A Phase II monotherapy study in relapsed refractory DLBCL is set to start early in the second half of the year. The company has also already moved forward with a Phase II study combining INCB50465 with Jakafi in myelofibrosis as well as proof-of-concept studies evaluating the candidate with the company's JAK1 inhibitor INCB39110 and Merck's PD-1 inhibitor Keytruda.

Leerink Swann's Schmidt said that he was "cautiously optimistic" about INCB50465.

Similarly cautious, JMP Securities analyst Lisa Bayko said in an April 18 note that the "question that remains on investors' minds is safety," pointing out that "although INCB050465 has structural modifications (removal of the purine group) that seem to dampen liver toxicity, infection risk will remain a class effect."

## COMPLEMENTARY APPROACHES

Across its pipeline, Incyte is focusing on development in two key areas: immunotherapy and targeted therapies aimed at cell growth and survival signaling, cooperative oncogenic pathways and cancer epigenetics.

In immuno-oncology, PD-1/L1 inhibitors decrease the immunosuppressive nature of the tumor environment, while agonists of GITR and OX40 work on co-stimulatory receptors on T-cells to enhance immune cell activity.

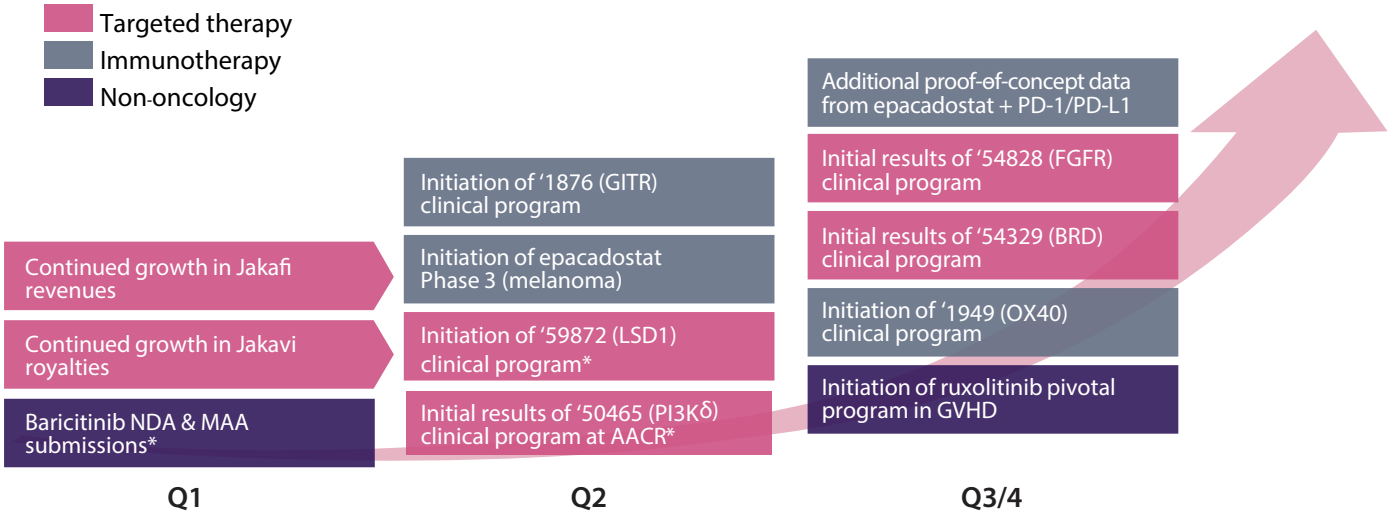
Preclinical data with GITR suggest that antibodies result in rapid and selective elimination of regulatory T-cells in the tumor, Peggy Scherle, VP of preclinical pharmacology, said during the call.

Very similar data have been reported with an OX40 antibody as well, she said. Furthermore, in vivo data suggest enhanced tumor growth inhibition when OX40 is combined with epacadostat.

"Mechanistically, we are still doing additional experiments to explore the mecha-

## Incyte's Coming Catalysts

Multiple Potential Value Drivers for Incyte in 2016




* Already completed

*Source: Adapted from Incyte's first quarter earnings presentation, May 9, 2016*

nistic underpinnings of these results, but the data would support that a greater efficacy will be observed with an agent that targets the T-cell directly in combination with one that targets the tumor microenvironment," she said.

The company is working with partner **Agenus Inc.** to move two candidates into the clinic – the GITR agonist INCAGN1876 and the OX40 agonist INCAGN1949 – both of which Scherle said are very selective and "bind very potently to their receptors."

A clinical study of INCAGN1876 will start within the next several weeks, CFO David Gryska announced during the first-quarter earnings call.

Jefferies analyst Brian Abrahams observed in an April 18 note that the company made a case that its GITR and OX40 antibodies are differentiated in that they have an IgG1 backbone. This feature enables cross-linking which can deplete regulatory T cells selectively, resulting in greater tumor shrinkage in preclinical studies, Abrahams noted.

"How this bears out clinically will help determine how well INCY can catch up with competitive programs further along in development. Synergy with PD-1 inhibitors and/or their IDO inhibitor epacadostat could speak to potential combination approaches down the line," the analyst said.

Phase I and II OX40 modulators include **Glenmark Pharmaceuticals Ltd.**'s GBR830 and **Bristol-Myers Squibb Co.**'s BMS-986178 and **AstraZeneca PLC**'s MEDI6469, according to the BioMedTracker database. Phase I and Phase II GITR agonists include Bristol's BMS-986256 **Novartis AG**'s GWN323 and AstraZeneca's MEDI1873.

### EXPLORING EPIGENETICS

The company also played up the potential of its targeted brododomain inhibitor INCB54329 during its AACR presentation.

A brododomain inhibitor led to "profound changes in cytokine levels, both in vitro and within the tumor microenvironment, so that a number of inflammatory cytokines were decreased in a dose-dependent manner," Scherle said.

The studies are still early, but this suggests "that there is a very strong synergy between epigenetic regulation and immunomodulatory agents," Scherle said.

The company is currently in Phase I with INCB54329. Huber said that work in the clinic has been focused on hematologic malignancies and tumor-directed therapy.

Incyte also announced during its earnings call that it just dosed the first patient in a study of an LSD1 inhibitor INCB59872, which has an epigenetic mechanism of action. (*See chart for major catalysts in 2016.*)

Incyte is starting to get a better appreciation for epigenetics and as "exciting target opportunities emerge there," it will think hard about them, Huber told "The Pink Sheet".

For now, the company is "starting to put in place a lot of the tools" needed to develop that unique class of targets, the exec said.

**DEAL WATCH** / A look at some of the most noteworthy recent biopharma transactions.

# Mylan Counts On A Renaissance For Expansion

*"The Pink Sheet" regularly covers business development and deal-making in the biopharmaceutical industry. Below is a roundup of some of the most noteworthy transactions that occurred between April 30-May 13. Deal Watch is supported by deal intelligence provided by* Strategic Transactions.

### MYLAN/RENAISSANCE

**Mylan NV** is bolstering its generic dermatology business with a deal that adds to the value of its previously-announced acquisition of Sweden's **Meda AB**, allowing the generics company to make up for its lost **Perrigo Co. PLC** opportunity.

The generics giant announced May 13 that it would be picking up the topical dermatology business from Renaissance Acquisition Holdings, a private holding of RoundTable Healthcare Partners, for $950m in cash plus another $50m in contingent payments. The deal is expected to close in the third quarter.

The deal gives Mylan a much larger presence in generic topical dermatology products – former acquisition target Perrigo has 50% of its generics portfolio in this space. The new portfolio includes more than two dozen topical products, as well as another 25 compounds in the pipeline. The deal also brings Mylan added infrastructure in the US and dermatology space along with a contract development and manufacturing organization. Mylan touted the 1,200 employees it would be integrating as well.

RoundTable will retain the sterile-focused part of the business and the associated manufacturing facilities.

While this acquisition will develop a space that Mylan has shown interest in for some time, the cost of the acquisition is a drop in the bucket. Mylan is among the many overly acquisitive companies that have often been criticized for racking up high debt levels as they pursue growth through M&A instead of organically. Yet, this acquisition will not add to the company's debt levels. Mylan has said that it will use cash on hand, as well as already established credit facilities, retaining its current debt-to-EBITDA ratio of 3.8 times.

The Renaissance portfolio had about $350m in sales in 2015, according to Mylan. Evercore ISI analyst Umer Raffat expects the deal will contribute about 19 cents per share to Mylan's 2016 earnings.

Mylan's last deal in the space – its $9.9bn purchase of Meda in February – was paid for with a combination of cash, debt and stock (*"Mylan Finally Nabs Meda In Diversification Play" — "The Pink Sheet" DAILY, Feb. 10, 2016*). Analysts and investors had been hoping that Mylan would do a "transformative" deal after its seven-month pursuit of Perrigo failed in 2015, when Mylan CEO Heather Bresch was highly criticized for the high price tag of the deal and its timing in a rocky market (*"Mylan And Perrigo:*

*Why Everybody Wins" — "The Pink Sheet" DAILY, Nov. 15, 2015*).

Both Meda and the Renaissance portfolio add to Mylan's business in a way that the company has been pursuing for a long time. While Mylan would've gotten much more had its $26bn acquisition of Perrigo succeeded, this is one of the key areas that Mylan was hoping to gain through that deal, meaning Mylan gets it at a drastically discounted price and will have a much smaller, easier company to integrate.

## PFIZER/WAVE LIFE SCIENCES

**Wave Life Sciences Ltd.** entered into a collaboration agreement with **Pfizer Inc.** for the discovery and development of nucleic acid therapeutics addressing five metabolic disease targets, adding $40m in upfront cash to its balance sheet that will help the newly public biotechnology firm keep its in-house focus on rare, genetic neurological and neuromuscular diseases.

Cambridge, Mass.-based Wave will add Pfizer's initial payment from the deal announced May 5, which includes a $30m equity investment, to a $196m stockpile that the company amassed in 2015, including $102m from an initial public offering in November and $78m from two separate venture capital rounds. The cash will fund Wave's operations into 2019, during which time it plans to take two new drug candidates into the clinic each year while out-licensing or possibly spinning out non-core programs into separate companies.

Wave President and CEO Paul Bolno said the company decided to develop therapies for neurological and neuromuscular indications on its own, because those are diseases where nucleic acid therapeutics can effectively provide systemic delivery to muscles and because genomic research is revealing new targets for rare diseases in those two areas.

"It's a great time to go into neurological rare diseases where the targets are more well-known," Bolno said. "We see hepatic diseases as an incredibly crowded space, so we wanted a partner with strong capabilities and Pfizer represented that strength in the metabolic space."

The Pfizer transaction has Wave executing its drug-development strategy in line with a plan that the company revealed to investors in January. That's when Wave first revealed that it would submit two investigational new drug (IND) applications to FDA each year and seek partners or consider spinout options for discovery and development programs in eye, liver, skin and gastrointestinal diseases.

In addition to the upfront fee, Pfizer will pay Wave up to $871m in research, development and commercial milestone fees plus tiered royalties up to the low single digits. The milestone payment total will depend on how many of the collaboration's programs Pfizer opts to license.

Wave will take up to five programs through discovery and clinical candidate selection at which point Pfizer will have a chance to exclusively license each of the programs. Pfizer will then take over all development and commercialization activities.

Two targets of interest to Pfizer have been declared, but only one of the targets has been identified publicly: apolipoprotein C-III (ApoC-III), which is a program that Wave already is working on preclinically. The other three targets will be identified within the next 18 months. Antisense and RNA Interference (RNAi) pioneers **Ionis Pharmaceuticals Inc.**, formerly known as Isis Pharmaceuticals, and **Alnylam Pharmaceuticals Inc.**each have lipid-lowering therapies targeting ApoC-III in late-stage development.

## IONIS/KASTLE

In its first collaboration, **Kastle Therapeutics LLC** acquired global development and commercial rights to Ionis' cholesterol-lowering medicine *Kynamro* (mipomersen) injection.

Under the deal announced May 3, Ionis receives $15m up front, a $10m milestone payment in May 2019, and up to $70m in sales milestones. Starting next year, Ionis will get global sales royalties in the low-to-mid teens (Strategic Transactions estimates 13%-16%). Ionis also receives a 10% common equity position in Kastle's parent company (assumed to be key backer VC firm Flexpoint Ford).

Under a January 2008 deal, **Sanofi**'s **Genzyme Corp.** obtained exclusive global rights to the drug but that agreement was terminated earlier this year. Genzyme will earn a 3% royalty on Kynamro sales and 3% of the cash payments Ionis receives from Kastle. Kynamro has FDA approval for homozygous familial hypercholesterolemia. Kastle was formed in July 2015 to acquire and develop drugs for high unmet needs.

## BRISTOL-MYERS SQUIBB/SELLAS

**Sellas Life Sciences Group**and **Bristol-Myers Squibb Co.** agreed May 2 to evaluate the combination of Sellas' galinpepimut-S with Bristol's *Opdivo* (nivolumab) in a Phase I ovarian cancer trial. Sellas recently initiated the trial at **Memorial Sloan Kettering Cancer Center** with ovarian cancer patients who are in at least their second remission. Galinpepimut-S is a Wilms tumor protein 1 (WT1) peptide vaccine in Phase II trials for mesothelioma, AML, myeloma and ovarian cancer (in addition to a preclinical study for brain tumor).

Opdivo, a PD-1 antagonist, is marketed for melanoma, non-small cell lung cancer and renal cancer; filed for approval for Hodgkin's lymphoma; and in a variety of preclinical through Phase II trials for additional cancers including head and neck, stomach, brain, liver, bladder and breast tumors, as well as leukemia and lymphoma.

## INCYTE/ARIAD

In conjunction with its May 9 acquisition of the firm's European operations, **Incyte Corp.** licensed exclusive rights to **Ariad Pharmaceuticals Inc.**'s *Iclusig* (ponatinib). Incyte will develop and sell the leukemia treatment in the European Union and 22 other countries, including Switzerland, Norway, Turkey, Israel, and Russia.

In addition to rights in the approved diseases, Incyte is paying $135m in development and regulatory milestones for work on the drug in new oncology indications (plus potential payments for non-oncology indications), plus tiered royalties between 32%-50%. The company will also fund some of the ongoing clinical development with Iclusig in two of Ariad's trials through cost-sharing payments of up to $14m ($7m in each of 2016 and 2017).

The deal includes an option for a future acquirer of Ariad to re-purchase the licensed rights from Incyte in exchange for fees equivalent to Incyte's payments (up-fronts, milestones, and development costs) and 20%-25% royalties. Iclusig is a BCR-ABL inhibitor (with activity against the T315I mutation) approved in Europe and other countries for chronic myeloid leukemia and Philadelphia-positive (Ph+) acute lymphoblastic leukemia.

Ariad is divesting rights to it (and to its entire **Ariad Pharmaceuticals (Luxembourg) SARL** division) in order to more effectively focus on commercializing Iclusig in the US. The drug was approved in the US in 2012 and last year brought in $112.5m in global net sales.

## VIFOR FRESENIUS/OPKO

**Opko Health Inc.** may have hit a setback for its vitamin D oral prohormone *Rayaldee* with an FDA complete response letter in March, but it has already gained an international marketing partner in **Vifor Fresenius Medical Care Renal Pharma Ltd.**, a common company of Galencia and **Fresenius Medical Care AG**. The Swiss firm will sell the secondary hyperparathyroidism treatment in Europe, Canada, Mexico, Australia, South Korea and certain other international markets. It also holds an option to acquire US rights for treatment of dialysis patients.

Under the agreement, announced May 9, Opko will receive an upfront payment of $50m, plus up to an additional $52m in regulatory and launch milestones, and $180m in sales-based milestones. VFMCRP will also pay Opko tiered, double-digit royalties on sales, and if it exercises the option for rights to the US dialysis market, will pay additional commercial-based milestones as well as double-digit royalties.

The partners will also collaborate to develop and commercialize Rayaldee for treatment of secondary hyperparathyroidism in dialysis patients.

The Rayaldee CRL was prompted by issues at a third-party manufacturer and were not specific to Rayaldee manufacturing (*"FDA Hold-Up: Opko Scrambles To Fix Problems At Manufacturing Site" — "The Pink Sheet" DAILY, March 30, 2016*). FDA accepted Opko's resubmission on April 22 and set a new user fee date of Oct. 22, 2016.

## ALEXA/GRUPO FERRER

Inhaled CNS drug biotech **Alexza Pharmaceuticals Inc.** looks set to be acquired by Spain's **Grupo Ferrer Internacional SA** in an all-cash offer that includes contingent value rights. The Barcelona-based, privately held mid-sized European pharmaceutical company has sweetened its latest move to acquire cash-depleted Alexza, announced May 10, by granting contingent value rights (CVRs) as well as $0.90 in cash for all of Alexza's shares.

It's an untidy turn of events for Mountain View, Calif.-based Alexza, which was founded by biotech pioneer and serial company entrepreneur Alejandro Zaffaroni, and is now being acquired by the ex-US licensee of its only marketed product, an inhaled formulation of the antipsychotic loxapine.

Ferrer might well be protecting its investment in Adasuve, but it is also acquiring an interesting research effort that could help extend its international ambitions that already include manufacturing and marketing pharmaceuticals, fine chemicals and generics in Europe, Latin America, Asia and the US.

In a May 10 statement, Ferrer CEO Jordi Ramentol expressed interest in continuing the development of Alexza's pipeline of development products: "We firmly believe the *Staccato* technology will change the lives of patients with severe mental and neurological disorders. At the same time it will help health care professionals to improve their management in the increasingly digitalized and personalized health care context."

The current move follows Ferrer's signing of a non-binding letter of intent to acquire Alexza in February. But the US company continued to explore two options for its future viability, either a buyout by Ferrer or the finding of a new US commercialization partner for Adasuve, after Alexza reacquired the rights from **Teva Pharmaceutical Industries Ltd.** during 2015.

But with only around $7.8m in cash and equivalents at the end of 2015, no new US licensee, and Adasuve only bringing in revenue of $5m during 2015, Alexza was expecting crunch time for the business to come at the end of April (*"Alexza's Last Stand: Hoping For Buyout Or License Of Adasuve" — "The Pink Sheet" DAILY, March 29, 2016*).

The share offer of $0.90 per share and one contingent value right per Alexza share entitles the holder to receive a pro rota share of up to four payment categories making the offer worth in aggregate up to a maximum amount of $35m if certain licensing and revenue milestones are met.

Ferrer's cash offer is at a 210% premium to Alexza's closing share price on Feb. 26, the last trading day before Ferrer's non-binding letter of intent. The offer is also a 177% premium to the volume-weighted average trading price over the previous 30 days before Feb. 26, and a 67% premium to the closing price on May 9. The transaction is expected to close in the second quarter of this year.

## THE MEDICINES CO./CHIESI

**The Medicines Co.** is selling off three cardiovascular products to Italy's **Chiesi Farmaceutici SPA**, the firm announced May 9, in an effort to raise funds to pay for R&D as its top-seller *Angiomax* continues to decline.

Chiesi will pay a total of $792m for three already-marketed drugs, including the newly approved *Kengreal* (cangrelor). The other drugs included in the deal are the antihypertensive *Cleviprex* (clevidipine) and the rights to the injectable direct thrombin inhibitor Argatroban. The Italian drugmaker will pay $260m upfront, as well as $480m in sales-based milestones. Chiesi will also assume the payment of $50m in milestone payment obligations and $2m for product inventory. The deal is expected to close in the third quarter.

TMC's best-selling product *Angiomax* (bivalirudin) lost patent protection in July 2015, opening it up to generic competition. Due to the influx of low-cost generics, the drug only brought in $16.9m in sales during the first quarter, down from $100.7m in the year-earlier period. More than half of TMC's revenue stream has been lost through the patent expiry.

The company believes the sale of these "non-core" assets will allow it to control costs and fund pipeline development. TMC said the divestiture will allow it to save between $65m to $80m in R&D costs and SG&A expenses. The move is in line with a restructuring announced last November. In December, the company divested three hemostasis products to Mallinckrodt PLC for $175m up front and agreed to $235m in milestone payments.

## SANOFI/MEDIVATION?

**Sanofi** has made a subtle statement that it is staying with its efforts to acquire **Medivation Inc.**, but is not at this time going to amend its offer. The French pharma announced May 13 it had filed a pre-merger notification under US Hart-Scott-Rodino antitrust requirements, with the offer of $52.50 per share, for an all-cash transaction valued at approximately $9.3 billion.

Medivation believes the offer is undervalued and has other interested bidders; there is speculation that **Pfizer Inc.** has moved into the lead.

Last week Sanofi had stated that if Medivation "engage[s] in good faith discussions with us and demonstrate[s] additional value, we could be in a position to revise our offer."

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# Recent And Upcoming FDA Advisory Committee Meetings

| TOPIC | ADVISORY COMMITTEE | DATE |
|---|---|---|
| Novo Nordisk's insulin degludec/ liraglutide injection as adjunct treatment to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus | Endocrinologic and Metabolic Drugs | May 24 |
| Sanofi's insulin glargine/lixisenatide injection fixed-ratio drug product and lixisenatide injection for treatment of adults with type 2 diabetes mellitus | Endocrinologic and Metabolic Drugs | May 25 |
| Teva Branded Pharmaceutical Products R&D Inc.'s hydrocodone extended-release tablets, formulated with purported abuse-deterrent properties, for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate | Anesthetic and Analgesic Drug Products; Drug Safety and Risk Management | June 7 |
| Pfizer's oxycodone/naltrexone extended-release capsules, formulated with purported abuse-deterrent properties, for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate | Anesthetic and Analgesic Drug Products; Drug Safety and Risk Management | June 8 |
| Merck Sharpe & Dohme's bezlotoxumab (MK-6072) for prevention of Clostridium difficile infection recurrence | Antimicrobial Drugs | June 9 |
| Development plans for establishing the safety and efficacy of prescription opioid analgesics for pediatric patients, including obtaining pharmacokinetic data and the use of extrapolation | Anesthetic and Analgesic Drug Products; Drug Safety and Risk Management; Pediatric | Sept. 15-16 |

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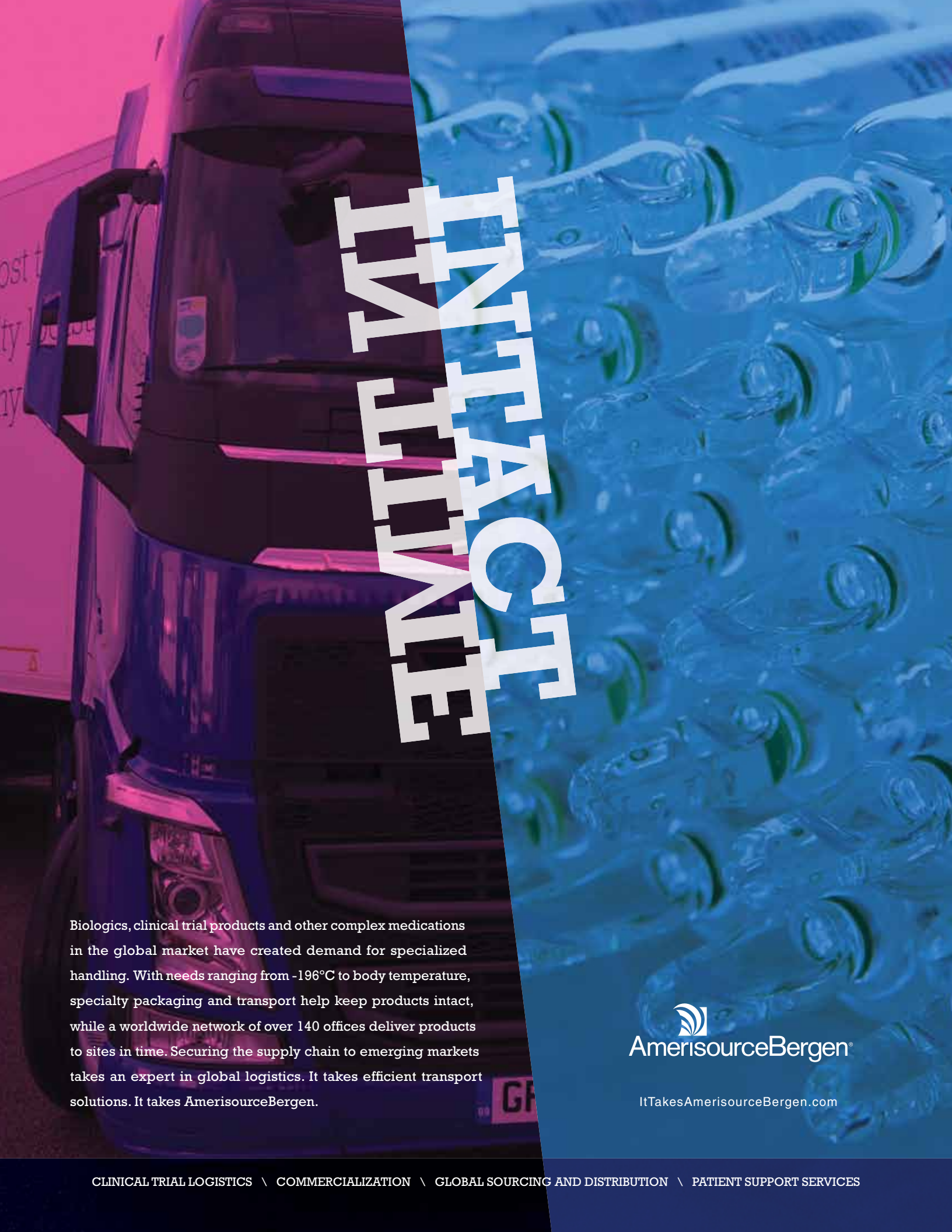


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