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US Supreme Court Permits Earlier Biosimilar Launches; Penalty For Declining Patent Dance Uncertain

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The US Supreme Court handed biosimilar sponsors a victory in ruling that they do not have to wait until FDA approval to provide 180-day notice of intent to market their products. But it remains to be seen if they could face an injunction under state law for not providing their application and manufacturing process information to innovator companies.

But the court's unanimous June 12 opinion in **Sandoz Inc.** v. **Amgen Inc.** gives industry only partial clarity on the implementation of the Biologics Price Competition and Innovation Act (BPCIA). It resolves the question of launch notification but raises a different question on the issue of whether sponsors must participate in the statute's information exchange process, known as the patent dance.

The court was asked if it was mandatory for sponsors to turn over their abbreviated biologics license application and manufacturing information, the first step in the exchange process. The court did not answer whether providing this information is mandatory though it referred to the exchange as a "requirement." Instead it ruled that innovator companies cannot seek an injunction under federal law to enforce this requirement while leaving open the possibility that they could obtain an injunction under state law. The court remanded the case to the Federal Circuit to decide whether the BPCIA preempts a state-law remedy for failure to provide the information.


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> "Whether Sandoz's conduct was 'unlawful' under the unfair competition law is a state-law question, and the court below erred in attempting to answer that question by referring to the BPCIA alone," Supreme Court says.

The parties had not asked the court to address the application of state law to the BPCIA but the justices honed in on this issue during oral arguments. Justice Neil Gorsuch asked what happens when there is a claim under state law that no one has argued is preempted. Assistant to the Solicitor General Anthony Yang, who argued on behalf of the federal government, replied that when you're complying with the federal statute there is no state law claim as the state law claim "is predicated on violating the federal law." *(Also see "FDA's Worst Case Scenario: Supreme Court Might Defer To It On Biosimilars" - Pink Sheet, 27 Apr, 2017.)*

Amgen expressed dismay at the decision. "While we are disappointed in the Court's decision on the notice of commercial marketing, we will continue to seek to enforce our intellectual property against those parties that infringe upon our rights," the company said in a statement.

Sandoz parent **Novartis AG** said the ruling on the notice of commercial marketing will help expedite patient access to life-enhancing treatments. "We also appreciate the clarity provided on the patent dance, which will help the biosimilars industry move forward," Eric Althoff, Novartis head of global media relations, said.

However, lawyers representing innova-

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Drug Pricing 'Deeper Dive' Planned By Senate Cmte. As Industry Avoids First Blood

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Hearings in July and the fall will follow, but if the first session was any indication, industry doesn't have anything to worry about.

AMR Threat Prompts EU, US And Japan To Join Forces To Align Data Requirements For New Drug Developers

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EU, US and Japanese regulatory agencies will provide advice to developers of antibiotics that is consistent with the agreements they have reached on aligning their data requirements.

Postmarketing Studies On Abuse-Deterrent Opioids Could Get New Look

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Data sources and methodologies to evaluate real-world effects of abuse-deterrent formulations will be focus of US FDA public meeting in July; value and feasibility of assessing the public health effects of such products more broadly is up for discussion.

PTAB Tosses Two More Humira Patents; Will Supreme Court Eliminate IPR Proceeding?

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Patent Trial and Appeal Board rules for Coherus in its challenge of Humira patents and takes up review of Cialis patent. US high court to consider constitutionality of inter partes review proceeding.

Repatha Pricing Pressure Might Actually Increase After Outcomes Trial

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Amgen's FOURIER study prompts ICER to plan new value-based price benchmark for Repatha below its previously recommended range of $5,404 to $7,735 per year.

Top Indian Official Hints At Drug Price Regulation To Curb 'Profiteering'

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A top Indian pharmaceutical department official says the government is determined to press ahead with its push for the prescription of more 'no-name' generic drugs in the face of a perception of profiteering by the pharma industry.

inside:

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tor companies said the ruling would create more uncertainty.

"The decision didn't provide the clarity the industry hoped for. It left open too many opportunities for gamesmanship," said Donald Ware, a partner at Foley Hoag who represented the Biotechnology Innovation Organization in its amicus brief in support of Amgen. He added that the ruling also "could lead to inconsistent outcomes" where a sponsor might be able to get an injunction to enforce the information exchange process under one state law but not another.

Ware said the decision leaves a lot of questions unanswered, such as how early can biosimilar sponsors give notice, when can a sponsor seek a preliminary injunction, and what happens if the applicant doesn't give any notice at all and fails to disclose its filing of an application for approval with the FDA. "This could lead to more at-risk launches of biosimilars and a less orderly process," he said.

> "The decision didn't provide the clarity the industry hoped for. It left open too many opportunities for gamesmanship." – attorney Donald Ware, who filed BIO's amicus brief

'DRAFTING LESSON' FOR CONGRESS

Amgen filed suit against Sandoz in October 2014 claiming its aBLA for *Zarxio* (figrastim-sndz), a biosimilar to Amgen's *Neupogen* (filgrastim), infringed its method of use patent and that Sandoz violated the BPCIA by failing to provide its application and manufacturing process information and providing early notice of intent to market the biosimilar. Amgen also claimed unfair competition for unlawful business practices under the California Business and Professions Code.

The US District Court of the Northern District of California ruled that Sandoz could decline to provide its application and manufacturing process information and give notice of intent to launch before FDA approval and it dismissed the state law claim.

In July 2015, a divided three-judge panel of the US Court of Appeals for the Federal Circuit agreed that the patent dance provisions are optional since the statute imposes consequences if the biosimilar sponsor fails to provide the information as the innovator can sue for infringement. But the panel found that Sandoz had to wait until FDA licensure of Zarxio to notify Amgen of its commercial marketing. The court also affirmed the dismissal of the state law claim finding that the remedies contained in the BPCIA are the exclusive remedies for an applicant's failure to comply with the information exchange.

The Supreme Court said a provision of the BPCIA provides a remedy when the biosimilar sponsor fails to provide this information, i.e., the innovator company can bring a declaratory judgment action for infringement. Given this remedy, and the absence of other specified remedies in the statute, Congress did not intend innovator sponsors to be able to obtain an injunction under federal law to enforce this disclosure, the court concluded.

Irena Royzman, a partner at Patterson Belknap Webb & Tyler who represents **Janssen Biotech Inc.** in Remicade (infliximab) biosimilar litigation, said the decision is "a drafting lesson for Congress."

"In order for a law to be enforceable, if Congress specifies any remedy or consequence, it needs to say" other remedies may be available, Royzman stated.

DOES BPCIA PREEMPT STATE LAW?

The court also disagreed with the Federal Circuit's finding that Sandoz's failure to provide this information was not "unlawful" under California's unfair competition law.

"Whether Sandoz's conduct was 'unlawful' under the unfair competition law is a state-law question, and the court below erred in attempting to answer that question by referring to the BPCIA alone," Justice Clarence Thomas wrote in the opinion for the court. "On remand, the Federal Circuit should determine whether California law would treat noncompliance with" the information exchange provision as "unlawful."

"If the answer is yes, then the court should proceed to determine whether the BPCIA pre-empts any additional remedy available under state law for an applicant's failure to comply with" the provision and whether Sandoz has forfeited any pre-emption defense.

William Jay, a partner at Goodwin Procter, said the preemption argument would be a strong one. If the federal government were to file an amicus arguing state law is preempted by the BPCIA, the Federal Circuit would take that quite seriously, he said.

INVITATION FOR FDA TO INTERVENE

Justice Stephen Breyer Issued a one-page concurring opinion. He said Congress had granted FDA the authority to interpret the terms of the BPCIA and suggested the agency's analysis could take precedent over the court's.

If FDA, "after greater experience administering this statute, determines that a different interpretation would better serve the statute's objectives, it may well have authority to depart from, or to modify, today's interpretation," Breyer wrote, adding that the court "need not now decide any such matter."

During oral arguments, Breyer repeatedly suggested that FDA resolve questions about the statute.

Asked for a response to Breyer's concurring opinion, the agency said "FDA will consider today's decision by the Supreme Court as it continues its efforts to implement the Biologics Price Competition and Innovation Act."

Ware noted that there have been proposals for FDA to require biosimilar applicants to certify that they have followed the BPCIA proceeding as a condition of getting approval. "With this decision defining the statutory requirements, FDA could now say it doesn't have to interpret the statute, just enforce it," he said.

WILL APPROVED BIOSIMILARS LAUNCH?

The court's ruling that biosimilar sponsors may provide marketing notice before receiving FDA approval could lead to the launch of two biosimilars that have been approved by FDA, **Samsung Bioepis Co. Ltd.**'s *Renflexis* (infliximab-abda), a biosimilar to Janssen's Remicade and Sandoz's *Erelzi* (etanercept-szzs), a biosimilar to Amgen's *Enbrel* (etanercept).

FDA approved Renflexis in April. At that time, **Merck & Co. Inc.**, which is launching the product in the US, said that under the BPCIA it could not launch until after the mandatory 180-day notice following FDA approval. *(Also see "Samsung's Renflexis: Second US Biosimilar To Janssen's Remicade, With A Few Firsts" - Pink Sheet, 22 Apr, 2017.)*

Merck said it is not commenting on the potential timing for the US launch of Renflexis in the wake of the Supreme Court's ruling. It is uncertain when Samsung first provided marketing notice.

Novartis said the decision will have no impact on Erelzi since it was approved in August 2016. As for the launch date, the company said it remains committed to bringing the biosimilar to US patients "at the earliest opportunity."

A third approved biosimilar yet to launch is Amgen's *Amjevita* (adalimumab-atto), a biosimilar to **AbbVie Inc.**s *Humira* (adalimumab). Amgen has said it does not expect to launch the product until at least 2018 given the complexity and pace of ongoing patent litigation.

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Neulasta Biosimilar From Coherus Needs Better Immunogenicity Assay After Stumble At US FDA

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US licensure of **Coherus BioSciences Inc.**'s pegfilgrastim biosimilar is likely to be delayed at least a year following FDA's request that the company reanalyze clinical immunogenicity data with a new, more sensitive assay.

On June 12, Coherus announced receipt of an FDA complete response letter for CHS-1701, a proposed biosimilar to **Amgen Inc.**'s *Neulasta* (pegfilgrastim), a pegylated leukocyte growth factor used as supportive care in cancer treatment.

Coherus said the letter primarily focused on FDA's request for a reanalysis of a subset of samples from a clinical immunogenicity study with a revised assay. The agency also requested additional manufacturing-related process information.

"FDA did not request a clinical study to be performed in oncology patients," the company said in a press release. Additionally, the letter "does not indicate additional process qualification lots would be required or raise concerns over the GMP status of CHS-1701 bulk manufacturing and fill-finish vendors."

During a same-day conference call, Coherus execs said they would seek a meeting with FDA to discuss the complete response letter. They predicted that the company would resubmit the application in about six months, with the FDA review taking up to another six months, meaning that approval would be unlikely before June 2018.

MORE SENSITIVE ASSAY NEEDED ...

The focus of FDA's attention is on study CHS-1701-04, a randomized, double-blind, two-period parallel study in 303 healthy subjects to assess immunogenicity and safety of two sequential 6 mg subcutaneous injections of CHS-1701 compared with two sequential 6 mg injections of Neulasta.

The primary objective was comparison of immunogenicity based on the development of neutralizing antibodies and the percent difference in anti-drug antibody (ADA) response. The company has previously announced the study met both prespecified endpoints: no neutralizing antibodies were detected in either group, and the percent difference in ADA response met the prespecified success criteria for biosimilarity.

Dennis Lanfear, Coherus' chairman and CEO, said FDA requested reanalysis of a subset of samples from the '04 study with a revised, more highly sensitive assay to confirm the robustness of the results.

FDA's letter described the parameters for the new assay, Lanfear said. "They were very specific and said, 'We would like an assay that performs like this.' … That is more refined and, I'd say, more optimized than the assay that we currently had in place."

"We will go ahead and we will begin our efforts to develop the assay – or refine the existing assays to the degree that they meet these new requirements," he said.

… BUT NO CALL FOR CANCER PATIENT STUDY

Responding to an analyst's question, Lanfear said the assay issue was unrelated to the company's decision not to perform an efficacy or immunogenicity study in oncology patients.

Coherus' development strategy was the focus of an April citizen petition by **Apotex Inc.**, which like Coherus has been stalled in its bid to bring a Neulasta biosimilar to market. Apotex said FDA should require that pegfilgrastim biosimilar sponsors conduct comparative efficacy or immunogenicity studies in the intended patient population because studies conducted only in healthy volunteers are not sufficient to show clinically meaningful differences from the reference product. *(Also see "Apotex Moves To Block Coherus' Neulasta Biosimilar; Asks FDA To Require Patient Studies" - Pink Sheet, 1 May, 2017.)*

> CEO Dennis Lanfear said FDA did not raise any issues about the pharmacokinetic/pharmacodynamic study conducted in 122 healthy subjects, "nor did the FDA ask us for an oncology study."

Coherus has asserted that Apotex misunderstands the role of clinical studies in biosimilar development and erroneously concludes that a specific type of clinical study is or is not required for licensure. *(Also see "Can Biosimilar Studies Be Conducted Solely In Healthy Volunteers?" - Pink Sheet, 16 May, 2017.)*

Lanfear said the agency did not raise any issues about Coherus' pharmacokinetic/pharmacodynamic study (CHS-1701-05), conducted in 122 healthy subjects, "nor did the FDA ask us for an oncology study in patients."

While the agency has not asked for a random sampling of subjects in the '04 study, Lanfear declined to disclose details about the subset of subject samples that will be reanalyzed "because the particular strategy that the company deployed in terms of the immunogenicity study is proprietary. And we have not previously disclosed such publicly, and we believe that this is a competitive advantage for the company. … There is a particular schema and approach that is used with that study, which employs a variety of assays."

MORE MANUFACTURING DETAILS

Turning to the other issue raised in the complete response letter, Lanfear said FDA requested "additional information regarding manufacturing procedures, release testing and other such details. We would categorize these requests as standard and consistent with expectations at this point in the review. These requests for detailed report summaries appear to us to be fully addressable with our existing data and experience."

However, the timing of the company's resubmission will depend upon the immunogenicity assay development and retesting, not the response on manufacturing issues, Lanfear said.

INDUSTRY 0-FOR-3 ON NEULASTA BIOSIMILARS

The complete response letter should not come as a surprise to anyone who has followed FDA's implementation of the biosimilar regulatory pathway.

FDA has said it would take the first biosimilar to a specific reference product to an advisory committee before approval. It has held true to this practice for all four of the first-in-class biosimilars approved to date. The fifth US-approved biosimilar, **Samsung Bioepis Co. Ltd./Merck & Co. Inc.**'s *Renflexis* (infliximab-abda), which is the second copy of **Janssen Biotech Inc.**'s *Remicade* (infliximab), skipped an advisory committee visit. *(Also see "Samsung's Renflexis: Second US Biosimilar To Janssen's Remicade, With A Few Firsts" - Pink Sheet, 22 Apr, 2017.)*

FDA never formally scheduled an advisory committee meeting for CHS-1701, which suggested the Coherus product was likely to suffer the same first-cycle regulatory fate as proposed pegfilgrastim biosimilars from Apotex Inc. and **Sandoz Inc.***(Also see "Pending Biosimilars" - Pink Sheet, 13 Feb, 2017.)*

Apotex's application, which had a user fee date in 2015, is understood to have received a complete response letter even though the company has never confirmed the letter or disclosed any details about a resubmission. *(Also see "FDA Met Biosimilar Review Timelines But Missed Meeting Goals In 2015" - Pink Sheet, 25 Apr, 2016.)* "Our file continues to be reviewed by the

> FDA never formally scheduled an advisory committee meeting for CHS-1701, suggesting the product was unlikely to be approved on first cycle.

FDA," an Apotex spokesperson said.

Sandoz's 351(k) application received a complete response letter in July 2016. Parent company **Novartis AG** has said it is conducting an additional study to address the agency's data request, and the application is expected to be resubmitted in 2018. *(Also see "Biosimilars: Sandoz Pegfilgrastim Review, Amgen Adalimumab Launch Extended To 2018" - Pink Sheet, 29 Oct, 2016.)*

Mylan NV and **Biocon Ltd.** will be the next biosimilar applicants to take a shot on the Neulasta goal; the partners' application for MYL-1401H was submitted in December and has an October use fee deadline.

In the analysts call, Lanfear was asked why pegfilgrastim has been such a tough nut to crack in terms of bringing a biosimilar to market, and whether the challenges have resulted from product's extended half-life and pegylation, which differentiate it from its predecessor agent.

Amgen's *Neupogen* (filgrastim) is the reference product for the first approved biosimilar in the US, Sandoz's *Zarxio* (filgrastim-sndz). The Supreme Court's June 12 decision in a closely watched case involving Zarxio could reshape how biosimilar applicants approach patent disputes and product launches.

Lanfear suggested two reasons why Neulasta biosimilar development has proven challenging: variation in terms of pharmacokinetics, and the presence of polyethylene glycol in other products.

"The clinical biology of this product makes it probably one of the more difficult biosimilars to advance," Lanfear said. "Typically, what you've seen with this molecule is high degree of variation with the patients in terms of the pharmacokinetic issues."

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In addition, the compound's polyethylene glycol tail "has its own potential immunogenicity issues … because there is endogenous peg antibodies flowing all through the population."

Given the presence of polyethylene glycol in toothpastes, body lotions and other products, people tend to become sensitized, Lanfear said. This is "probably a complicating factor in terms of parsing through immunogenicity of pegfilgrastim molecules, which you don't get with a simple, straightforward sequence molecule like filgrastim."

While simplicity has eluded filgrastim biosimilars so far, the first successful applicant will likely find itself not only enjoying a lucrative market, but a lot of regulatory knowledge that could be applied to other more complicated biologics as well.

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Taking Biosimilars Down A PEG: Why Copying Neulasta Isn't So Easy

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When the biosimilar pathway was enacted in the US, there were some shared assumptions about which products might be first to win FDA approval using the abbreviated pathway, and which might take more time.

Relatively "simple" proteins would surely be the first ones through – with filgrastim (**Amgen Inc.**'s *Neupogen*) and epoetin (Amgen's *Epogen*/**Johnson & Johnson**'s *Procrit*) – at the top of the list. Monoclonal antibodies would likely take longer, given the significantly greater complexity of those molecules.

Somewhere in between would fall longer-acting, pegylated proteins. Like Amgen's *Neulasta* (pegfilgrastim).

So far, those assumptions haven't proven very accurate. The first 351(k) biosimilar approval was indeed for a "simple" product, **Sandoz Inc.**'s copy of filgrastim. The first EPO biosimilar should be coming to market soon: **Pfizer Inc.**'s version cleared an FDA advisory committee and has a user fee goal date later in June. *(Also see "Pfizer Excludes EU Biosimilar Experience From US Epoetin Application" - Pink Sheet, 5 Jun, 2017.)*

But in between, there have been several more complex biosimilars approved, starting with Pfizer/**Celltrion Inc.**'s copy of J&J's *Remicade* (infliximab), followed by versions of Amgen's *Enbrel* and **AbbVie Inc.**'s *Humira*, along with a second copy of infliximab. And hard on the heels of the likely EPO approval will be two more monoclonal antibodies, with versions of **Genentech Inc.**'s *Avastin* and *Herceptin* headed to the advisory committee stage in July. *(Also see "Biosimilars For Avastin, Herceptin To Cap Off Busy July For ODAC" - Pink Sheet, 7 Jun, 2017.)*

So, at least based on the first approvals, it turns out that monoclonal antibodies weren't all that much harder than the "simple" proteins.

Which leaves the pegylated products, so far notably absent from the list – especially now that the third attempt at approval has been rejected by FDA. **Coherus BioSciences Inc.** announced June 12 that it received a complete response letter for its application, joining **Apotex Inc.** /**Intas Pharmaceuticals Ltd.** and Sandoz in having been sent back for more work on the product. *(Also see "Neulasta Biosimilar From Coherus Needs Better Immunogenicity Assay After Stumble At US FDA" - Pink Sheet, 12 Jun, 2017.)*

Given that filgrastim was the first molecule through the pathway, why is it so hard to get pegfilgrastim through? After all, the "PEG" in pegfilgrastim, is just polyethelene glycol – a chemical used in countless consumer products from toothpaste to skin creams to paintball filler. If a sponsor like Sandoz can copy a complex medicine like filgrastim, adding PEG to the formulation should be relatively simple. Right?

It turns out, however, that while PEG may be ubiquitous, it is anything but simple.

Coherus offered some thoughts on that point during a conference call explaining the complete response letter.

FDA officials repeatedly pushed back on efforts to assert any general safety of PEG based on experience with other products and formulations.

Given the presence of polyethylene glycol in consumer products, people tend to become sensitized, CEO Dennis Lanfear explained. This is "probably a complicating factor in terms of parsing through immunogenicity of pegfilgrastim molecules, which you don't get with a simple, straightforward-sequence molecule like filgrastim."

FDA has also offered some insights into the challenges of pegylated products, albeit in a very different context: the April 4 review of **Novo Nordisk AS**'s pegylated Factor IX clotting factor *Rebinyn*.

FDA convened the committee to discuss concerns about the potential risks of neurocognitive adverse effects based on PEG-accumulation seen in animal models. Throughout that meeting, FDA officials repeatedly pushed back on efforts to assert any general safety of PEG based on experience with other products and formulations.

At least in that context, FDA was unwilling to accept that the widespread chronic exposure to PEG in other classes of therapies could help provide assurance of safety from long-term exposure to the Novo clotting factor. As a result, the product was approved solely for acute use to control a bleeding episode, not for chronic long-term prophylactic use where the longer acting formulation would seem more relevant. *(Also see "Novo Nordisk Gets Approval For Hemophilia B Treatment Sans Postmarketing Requirements" - Pink Sheet, 3 Jun, 2017.)*

FDA's explanation for taking that position is worth quoting:

"There are many marketed products that are glycoPEGylated," Office of Tissues & Advanced Therapies Director Wilson Bryan told the advisory committee. "Because of differences between those products and among these glycoPEGylated products, including the molecular weight of the PEG, the pharmacokinetics, the route of administration, the duration of administration – because of these variety of differences, the relevance of the preclinical and clinical and postmarketing experience of these other products to the Novo Nordisk product is unclear."

That discussion – and the early experience by would-be biosimilar sponsors – suggests that PEG-formulations may be anything but simple.

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Innovation The Big Winner As China Joins ICH

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Global drug development issues are finally making waves in China, a vast country that has so far produced relatively fewer innovative new therapies than other major markets such as the US and Europe.

Now, China is stepping up to that challenge, announcing one move after another in recent months to try and change the situation. The latest and potentially most influential move by the country is a decision to join as a full member the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), an organization that brings regulators and the industry together to discuss and set such rules for drug registration and use.

The step, announced in late May, has many cheering the prospect of an accelerated pace of new drug approvals in China. Previously, due to a lengthy regulatory timeline and cumbersome "three filings, three approval" process, sponsors of new drugs often had to wait three to five years just to get clearance to start clinical studies in China, but now they are looking to start parallel studies with the US.

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CHINA'S JOURNEY TO THE ICH:

2010: CFDA issues ICH common technical document (CTD) guidelines.

2012: CFDA issues safety report guidelines using ICH Periodic Safety Update Reports for Marketed Drugs (PSUR).

2015: CFDA issues stem cell development guidelines based on ICH Guidelines for Viral Safety Evaluation of Biotechnology Products Derived from Cell lines of Human or Animal Origin-Q5A(R1)-1999.

2017: CFDA sets ICH membership as its work priority for the year.

HISTORIC MILESTONE

The move is significant in that ICH has so far accepted memberships from other major pharma regulatory agencies in the EU, US, Japan, and Canada, along with Switzerland, Brazil and South Korea, while Taiwan is among the observers in the organization.

Although the China FDA said the joining decision is still pending final formal clearance from China's Ministry of Foreign Affairs, many are already characterizing the major step forward as a historic milestone.

The first real early indication of China's intention to join the ICH came in May, when CFDA Commissioner Bi Jingquan met Dr. Teresa Mullin, director of strategic programs at the US FDA's Center for Drug Evaluation and Research (CEDR), and deputy chair of the ICH.

"It feels like China joining the WTO [World Trade Organization] the second time," claimed Dan Zhang, founder and CEO of Fountain Medicines Development Co. Ltd, a Beijing-based contract research organization (CRO).

The entry into WTO in 2001 allowed China to gain access to international technical knowhow and tap into foreign investment, propelling the country to become the second-largest economy in the world in little over a decade.

Joining the ICH is likely to give another boost to new development in the country, Zhang noted, adding that among the many benefits, one notable advantage would be the simultaneous development of new drugs, helped by the existing ICH guidance and initiatives in this area.

Many observers also expect to see more harmonization of the CFDA's regulations with global norms, including the ICH Q1 guideline for API stability requirements, the Q7A guidance for API plant GMP inspections, E6 for GCP requirements, and E17 governing multi-regional clinical trials.

MORE PARALLEL FILINGS

Already, as many as seven investigational new drug (IND) study applications are being filed in China as well as the US, Zhang noted.

Such simultaneous development is expected to benefit both international drug firms and domestic innovative startups who are eager to tap into China's vast patient population.

Multinationals are already re-positioning themselves for the change, with some changing business models while others are looking to register and launch new products in China quickly and cost-effectively.

During a recent industry meeting, local executives of Merck, Pfizer, Roche and Sanofi pointed to the recent and upcoming regulatory changes and emerging new technologies as catalysts for new models in China.

"Mid-sized and small companies are also eager to leap into the fray," Fountain's Zhang noted. Constrained by their limited resources, they are now able to outsource manufacturing to contract manufacturing organizations, thanks to the CFDA's marketing authorization holder pilot program.

That translates into lowered technical barriers and accelerated registration and launch of imported products in China, giving patients access to new therapies, and allowing CROs to expand their business in both China and overseas markets.

Patients, CROs, and all innovative firms are thus slated to gain big, said Zhang during a presentation on June 8.

INCREASED OPTIONS

The ICH will open doors and give innovative new drug developers more options in China, Zhang predicted. Before, most companies focused on developing therapies for the local market, and such an "in China, for China" strategy positioned projects for government support and fast-track approval pathways.

With a more harmonized regulatory environment, companies may choose to develop global first-in-class drugs, abbreviated 505b(2) products, or orphan products.

Developers should even be able to file new drug approvals (NDAs) in China before outside, which was unthinkable before. Up to now, only new drugs that have entered Phase II studies overseas could apply to start clinical trials in China.

In addition, "Foreign drug makers will be more likely to include China sites in their global drug development planning," Zhang said.

QUALITY FOCUS

Despite these positive prospects, Zhang added that the adoption of ICH standards in China will be gradual, and that companies must prioritize training with a keen focus on quality assurance.

"[New products' entry to China] depends on the speed of adoption of ICH technical documents, it also depends on reimbursement and commercial insurance," he said.

Meanwhile, study sponsors must ensure the quality of their clinical study data, given the challenges of finding GCP-compliant study centers and experienced clinical study teams in China.

Additionally, quality assurance and quality control training is particularly important, as is routine review of standard operating procedures, he noted.

The relationship between China and the ICH will thus be an evolving one. Before entering China, companies still must consider what types of products and unmet medical needs they want to address. Only with customized information and personalized design can a company succeed in the fast-changing environment in the country, Zhang concluded.

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Value & Pricing Perspectives From ASCO, In Brief

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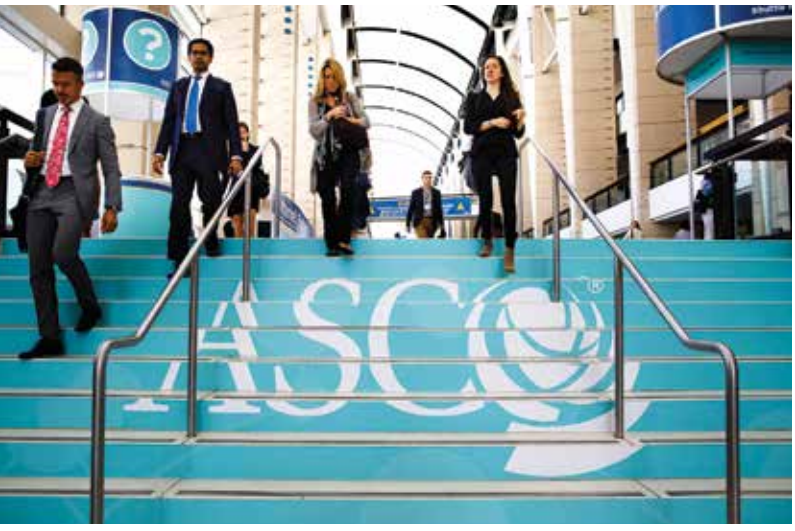

Photo credit: ASCO

Round-up of commentary on oncology drug value and costs during the American Society for Clinical Oncology annual meeting, including value frameworks, ways to lower drug costs and payer data.

ASCO, ESMO VALUE FRAMEWORK COMPARISONS

Comparisons between cancer drug value frameworks developed by the American Society for Clinical Oncology framework, the European Society for Medical Oncology (ESMO) and other groups should take into account the fact that the tools have differing purposes, suggests Lowell Schnipper, chief of oncology/hematology at Beth Israel Deaconess Cancer Center and head of the ASCO Value in Cancer Care task force.

A difference in targeted end users may contribute to a difference in the valuations produced, he suggested at the ASCO annual meeting June 3. ASCO's framework is designed to aid prescribing

"Our first several iterations really focused on the patient and not so much the policy, although the policy issue looms large in our minds as a different but similar adaptation for our framework."
– ASCO task force head Lowell Schnipper

decisions between physician and patients, while the ESMO Magnitude of Clinical Benefit Scale is a more policy-oriented tool, Schnipper pointed out. In line with that focus, the ASCO framework put more of an emphasis on progression-free survival than the ESMO framework does, he noted.

"We are beginning to see manuscripts that appear to say our value assessments don't always agree," he said. "That isn't very surprising. …We are not fully aligned and should we be? That's really the issue," he commented. "Should there be different frameworks for different purposes? My answer to that is probably … since those issues that are important to the patient in front of me are not likely to be parallel with those that are relevant to all of society" especially "in the world of individual choices, as is the case in the US."

According to a comparative analysis presented by Sierra Chang and published in the *Journal of Clinical Oncology* June 3, the ASCO value framework and ESMO-MCBS had "weak to moderate" correlation and the clinical benefit scores under ASCO's framework did not correlate with the incremental QALYs or funding recommendations from pCODR (the pan-Canadian Oncology Drug Review) or the UK's NICE (National Institute for Health and Care Excellence) – "suggesting different 'constructs' of clinical benefit are being measured." Chang suggested "the context and definition of 'clinical benefit' may require further consideration in order to reach a common understanding and consensus across all stakeholders."

ASCO may consider revising its value framework in the future so it can be used as more of a policy tool, Schnipper suggested in his talk the next day. "Our first several iterations really focused on the patient and not so much the policy, although the policy issue looms large in our minds as a different but similar adaptation for our framework."

Meanwhile, "ASCO continues to assess and refine the society's value framework and its methodology to best meet the needs of the oncology community," a spokesperson said in an email. "To that end, we plan to test the framework further through modelling and identifying additional improvements that may be needed. Next steps for the framework will be determined following that testing process."

One modification the group has struggled with is incorporating more of a patient perspective on value in the framework. *(Also see "ASCO Cancer Drug Valuation Tool Will Incorporate Patient Preferences" - Pink Sheet, 31 May, 2016.)*

Schnipper suggested other issues worth considering include whether the framework sets the bar "high enough" for effectiveness. Many cancer drugs "have only a very modest incremental benefit in survival. We need to think about whether we need to raise the bar far higher than it currently is." He also noted that while the framework's focus on cost relates primarily to patient out-of-pocket spending, "it is legitimate to consider a much broader impact on health care costs of a given therapy in order to be most fair to it."

The ESMO scale is also undergoing revisions. "Version 1.1," which will be published in the *Annals of Oncology* in September, will add consideration of single-arm trials for treatments of orphan diseases or those with high unmet need.

CANCER RESEARCHER CONSORTIUM TO FOCUS ON LOWERING DRUG COSTS

A group of oncology researchers is planning a series of randomized clinical trials aimed at identifying changes in oncology drug prescribing that could lower costs. Led by former ASCO CEO Alan Lichter, the Value in Cancer Care Consortium plans to study whether lower, and less expensive, dosing could be just as effective as higher doses used in pivotal clinical trials.

The initiative is viewed as the most "readily actionable" way to reduce cancer drug costs for patients without the need for regulation or legislation, according to the organization. "For practices, as we enter the era of value-based care and financial risk sharing, [we] will have to lower costs from year to year. Understanding where one can do so without compromising quality of care and outcome will be crucial," the consortium says in an overview of its mission.

A Phase II "proof of concept" study evaluating the food effect on the pharmacokinetics and pharmacodynamics of **Janssen Pharmaceutical Cos.**'s prostate cancer treatment *Zytiga* (abiraterone) found that one-fourth of a dose with food is not inferior to a standard dose fasting. Presented at the ASCO Genitourinary Symposium earlier this year, the study was conducted by University of Chicago researcher Russell Szmulewitz. **GlaxoSmithKline PLC**'s *Votrient* (pazopanib) may be another candidate for such a study, the consortium suggests.

The consortium also plans to study whether a lower-priced agent could substitute for a higher-priced drug and whether duration of therapy could be adjusted to save money. Possibilities for an interchange evaluation include paclitaxel versus **Roche**'s *Abraxane* (nab-paclitaxel) and irinotecan versus **Ipsen**'s *Onivyde* (nal-irinotecan) in pancreatic cancer and sirolimus versus **Novartis AG**'s *Afinitor* (everolimus) in different indications.

Duration of therapy studies could focus on using less drug through less frequent dosing, such as administering **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) every four weeks versus every

two weeks. Another approach would be using less drug through shorter durations of treatment, such as by using a PD-1 or PD-L1 inhibitor for six months versus 12 months. A plan for research will be determined in the coming months by the group's scientific advisory committee, chaired by Ian Tannock, University of Toronto, and Gabriel Hortobagyi, MD Anderson Cancer Center.

UNITEDHEALTHCARE TO POST ONCOLOGY TREATMENT DATA

Starting in 2018, **UnitedHealthCare** will post information on real world experience with oncology drugs on a public website using four measures:

1. How long treatment lasted or how long it worked;
2. The hospitalization rate associated with treatment;
3. Total cost of care incurred per patient; and
4. Regimens being selected most often.

"We won't express a judgment about those but we'll put the data in front of the physician and the patient who is interested and they can use it in their decision making," UnitedHealthcare Senior VP Oncology and Genetics Lee Newcomer reported during a June 4 session at ASCO. "We want to create transparency in that space."

Newcomer was also co-author on a study using claims data to assess the comparative value of common first-line non-small cell lung cancer regimens in a real world setting. The retrospective analysis used clinical data from a prior authorization program for chemotherapy – including cancer type, stage at diagnosis, biomarkers, treatment line and evidence of progression/relapse – linked with administrative claims data. The abstract notes that "patients treated with the five most commonly prescribed first-line therapies for mNSCLC have much shorter duration of therapies (52-76 days) than reported in published clinical trials with a significant risk of hospitalization (18%-30%) and at substantial cost ($34,971-$108,100)." Of 830 patients reviews, 345 initiated carbo/cisplatin + pemetrexed, carbo/cisplatin + paclitaxel, carbo/cisplatin + bevacizumab + pemetrexed, nivolumab, and docetaxel. The authors note that the data will become more valuable as the database grows over time.

US GOVERNMENT COVERAGE MANDATES INHIBIT VALUE-BASED DECISIONS

Removing government mandates that all FDA-approved oncology drugs be covered could help reduce the "financial toxicity" involved with oncology treatment, according to UnitedHealthcare Senior VP Oncology and Genetics Lee Newcomer. "If you are in a program like Medicare or Medicaid or commercial insurance in 42 different states in this country, you are mandated to provide coverage for any FDA approved cancer medication," regardless of price, value or outcome, he said. "That destroys the whole idea of an economic interchange. We can't use value in making decisions," he maintained. "Where there are multiple regimens, we should be allowing competition to get back in the marketplace so we can provide access to good therapies and still keep money available for those new innovations that are coming down the pike."

For programs like Medicare or Medicaid or commercial insurance in most states, "you are mandated to provide coverage for any FDA approved cancer medication," regardless of price, value or outcome. "That destroys the whole idea of an economic interchange." – UnitedHealthcare's Lee Newcomer

COMPANY PAYMENTS HAVE IMPACT ON PRESCRIBING

Observational research presented at ASCO by Aaron Mitchell, University of North Carolina, found a "consistent association between receipt of general payments from industry and increased prescribing of that company's drug." Mitchell noted such payments are "entirely legal, but controversial." The study used the Medicare Part D Prescriber Data and the Open Payments database to test the association between payments from a pharmaceutical company and physician usage of that company's cancer drug (limited to oncologists with at least 20 filled claims for the drugs of interest).

The study concentrated on cancers where there are multiple oral options: sunitinib (**Pfizer Inc.**'s *Sutent*), sorafenib (**Bayer AG**'s *Nexavar*) and pazopanib (**Novartis AG**'s *Votrient*) in renal cell carcinoma, and imatinib (Novartis's *Gleevec*), dasatinib (**Bristol-Myers Squibb Co.**'s *Sprycel*) and nilotinib (Novartis's *Tasigna*) in chronic myeloid leukemia.

The median value of all general payments – including sponsored meals, consulting, speaker fees, travel/lodging and gifts – was $566 for the RCC cohort of 356 physicians and $166 for the CML cohort of 2,140 physicians. Research payments in the form of direct research grants and funding to the institution averaged to $33,391 for RCC and $185,763 for AML. While the consistent association of prescribing and general payments was seen across multiple sensitivity models, there was inconsistent association for research payments and prescribing.

Mitchell acknowledged certain limitations of the study, including the accuracy of the data, generalizability, indications for other cancer types and that its shows only correlation. Discussing the findings, University of Pennsylvania's Erin Aakhus added that the cohort was biased towards prescribers from large practices, which may have a disease focus, and there was no breakdown of community or aca-

demic settings. She also suggested it was "possible or plausible that oncologists with a preference for a certain drug are more likely to receive payments, perhaps not the other way around." However, she concluded, "as we engage in discussions about value, the influence of the manufacturer on decision making needs to be considered."

CLINICAL BENEFIT AND DRUG PRICES DON'T TRACK

The link between drug prices and clinical benefit continues to draw scrutiny. Ronak Saluja, Sunnybrooke Health Sciences Centre, presented data at ASCO on the relationship between the cost of novel oncology drugs and their clinical benefit over time. "The average launch price of oncology drugs has increased by 10% annually from 1995 to 2013," Saluja and colleagues observed. "The purpose of this study was to determine if the clinical benefit of novel oncology drugs has increased proportionally over time and is correlated with launch price.

The study identified novel oncology drugs with randomized controlled trials approved from January 2006 through August 2015; clinical benefit was scored using the ASCO Value Framework and the ESMO Magnitude of Clinical Benefit Scale. Launch prices were based on RedBook and the 28-day cost was determined from the trial's dosing schedule and adjusted using the 2015 consumer price index. Forty clinical trials were reviewed, but the study did not indicate pricing corresponded to clinical benefit. "The rising cost of novel oncology drugs over time is not associated with an increase in their clinical benefit, suggesting a decrease in their value over time," the researchers concluded.

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Valproate In The Spotlight As EMA Releases Date For First Ever Public Hearing

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The European Medicines Agency will hold its first ever public hearing on the safety of marketed medicines on Sept. 26 to review the use of valproate-containing medicines in the treatment of women and girls who are pregnant or of childbearing age.

The public hearing, to be held by the EMA's Pharmacovigilance Risk Assessment Committee, will mark the first time that EU citizens will be given a voice in evaluating the safety of medicines on the market.

Valproate-containing medicines are approved nationally in the EU to treat epilepsy, bipolar disorder and, in some countries, migraine, but have been linked to the risk of malformations and developmental problems in babies who are exposed to drug in the womb. While other treatment options are available, sometimes the only effective treatment for a woman is valproate and in those cases usually the risk to the unborn child of not treating the condition is higher than the risk posed by the medicine.

The agency first announced in March that it would be holding the hearing and said the precise date of the hearing would be decided in June. Further information, including a list of specific questions on which information from the public is sought, a summary of the safety concerns, as well as practical information on how to participate and an application form, will be published at the beginning of July.

The EMA's first ever public hearing has been some time coming. The agency was given the authority to hold hearings under the EU pharmacovigilance legislation in 2012. It adopted the rules and procedures for such hearings in April last year, and has carried out simulation training.

Last year, a senior EMA official indicated that the agency would not start the hearings until it had found the perfect case – i.e., one where collecting the views of the public would really bring added value to the EMA's review. *(Also see "Waiting For The Perfect Case: Why EMA Has Yet To Hold A Public Drug Safety Hearing" - Pink Sheet, 6 Dec, 2016.)*

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> Views from the public "will bring a unique new dimension to the assessment of medicines by the PRAC" – EMA

"Public hearings will give EU citizens a voice in the evaluation of the safety of medicines and empower them to express their views on issues related to the safety of certain medicines and the management of risks," the agency said. "Their views will bring a unique new dimension to the assessment of medicines by the PRAC for the benefit of public health."

As for valproate itself, the EMA in 2014 ordered stronger warnings and restrictions on the use of the drug in women, due to the risk of malformations and developmental problems in babies who are exposed to valproate in the womb. *(Also see "EMA to go extra mile to facilitate joint safety study for valproate" - Pink Sheet, 12 Feb, 2015.)*

Following concerns over the effectiveness of these measures, the French medicines agency, ANSM, asked the EMA to re-examine the matter and consider whether further EU-wide action should be recommended to minimize risks in women who are pregnant or of childbearing age.

As part of this review, the PRAC decided to organize a public hearing "to listen directly to the experience of EU citizens with these medicines" so this can be taken into account in PRAC's final recommendation, according to the EMA.

In April this year, ANSM released new study results confirming the "highly teratogenic nature" of valproate when used for the treatment of epilepsy and bipolar disorder in women during pregnancy, with as many as 4,100 French children potentially having suffered major birth defects since the drug's launch in 1967.

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Opana Withdrawal Request Builds On US FDA Actions On Palladone, OxyContin

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The US FDA's decision to seek market withdrawal of **Endo Pharmaceuticals Inc.**'s *Opana ER* (oxymorphone extended-release) due to intravenous abuse liability builds upon earlier regulatory actions on two **Purdue Pharma LP** opioid products and may be the beginning a new level of scrutiny for opioid product formulations with high risk of abuse.

The agency's 2005 request that Purdue withdraw *Palladone* (hydromorphone extended-release) due to the risk of dose-dumping in the presence of alcohol and its 2013 conclusion that the original formulation of *OxyContin* (oxycodone extended-release) was removed from the market for safety reasons may have laid the groundwork for its decision to request Opana ER's withdrawal.

In all three cases, use of the drugs in a manner inconsistent with labeling led FDA to conclude that the products' benefits no longer outweighed the risks, even for the intended population.

"I would point to Palladone and OxyContin to sort of paving the way for the action FDA took" on Opana ER, said Sheldon Bradshaw, a former chief counsel who is now a partner at the law firm King and Spalding.

Given the enormous public health concerns about the opioid epidemic and newly installed Commissioner Scott Gottlieb's vow to make addressing opioid abuse his top priority, other companies may soon find themselves facing the same choice as Endo: withdraw a product, or continue marketing it despite FDA's public declaration that it is unsafe.

> In the case of Palladone, original OxyContin and now Opana ER, use of the drugs in a manner inconsistent with labeling led FDA to conclude that the products' benefits no longer outweighed the risks.

PRECEDENT FOR 'FIRST TIME' ACTION

FDA announced June 8 that is has requested Endo remove Opana ER from the market because the drug's benefits no longer outweigh its risks. The decision stems from epidemiological data suggesting the reformulation of the drug in 2011 led to a shift in the preferred route of abuse from intranasal to intravenous, which has been associated with cases of HIV transmission and thrombotic thrombocytopenic purpura. *(Also see "Opana ER Should Come Off The US Market, FDA Tells Endo" - Pink Sheet, 9 Jun, 2017.)*

The agency's negative conclusion on Opana ER's risk/benefit profile was in lock-step with a majority of advisory committee members at a March meeting. However, most of the external experts favored labeling restrictions and a tougher Risk Evaluation and Mitigation Strategy, with only a minority calling for the drug's withdrawal. *(Also see "Opana ER Looking At REMS – Or Worse – After US FDA Panel Weighs Intravenous Abuse Risk" - Pink Sheet, 14 Mar, 2017.)*

Endo said it is evaluating its options but has not announced whether it will withdraw the long-acting opioid. However, the company noted the action is based on safety issues resulting from misuse and abuse of the drug, not from its approved use in appropriate patients.

FDA's statement on the requested withdrawal said it marked the "first time the agency has taken steps to remove a currently marketed opioid pain medication from sale due to the public health consequences of abuse."

However, there is some precedent in the Palladone and OxyContin examples for the action FDA is now pursuing on Opana.

Purdue pulled Palladone off the market in July 2005 at FDA's request after data showed that the extended-release formulation was compromised when the drug was used with alcohol, leading to "dose dumping," or the rapid release of active ingredient. At the time of Palladone's removal, FDA emphasized that its withdrawal request was based on safety concerns related to Palladone's intended use, not the potential for abuse. *(Also see "Purdue Withdraws Palladone; FDA Evaluating Other Extended-Release Opiates" - Pink Sheet, 18 Jul, 2005.)*

However, the drug's original labeling warned against use with alcohol. In the case of Palladone, "it was primarily unintentional abuse," Bradshaw said. "It was sort of misuse because it was still using the product outside of the labeling mechanisms."

The agency also may have felt constrained in its ability to seek a product's removal due to intentional misuse and abuse because the Palladone withdrawal happened two years before the 2007 passage of the FDA Amendments Act, which gave the FDA new drug safety powers.

However, FDA's 2013 determination about the safety of the original OxyContin formulation was grounded in the product's abuse liability.

Purdue reformulated OxyContin with physicochemical properties intended to make abuse by the intranasal and intravenous routes more difficult. In April 2013, FDA determined that the original formulation was withdrawn from sale for reasons of safety or effectiveness and, consequently, generics referencing original OxyContin could not be approved. *(Also see "OxyContin Revised Labeling Expects Less Abuse Via Injection, Snorting" - Pink Sheet, 16 Apr, 2013.)*

> "The writing is now on the wall that if you have a product that can be abused and there are alternatives to that product that are similarly efficacious, you may soon be coming off the market." – King and Spalding's Bradshaw

FDA concluded original OxyContin had the same therapeutic benefits as the reformulated version but "poses an increased potential for abuse by certain routes of administration, when compared to reformulated OxyContin."

Bradshaw said that in the case of OxyContin, "the company voluntarily initiated the withdrawal rather than responding to an FDA request, but it is yet another example of an opioid being withdrawn from the market for safety reasons because of its potential for abuse."

He pointed to statements in FDA's OxyContin determination about how the agency views a drug's abuse potential as part of the overall benefit/risk determination.

"FDA has long considered the abuse potential of a drug in numerous regulatory contexts. Where appropriate, FDA may take into account abuse potential as part of the safety profile of a drug when weighing its benefits and risks," the agency said in the Federal Register notice announcing the OxyContin determination.

FDA has "long considered the question of abuse as one of the factors in determining the safety profile of the drug as they weigh the benefits and the risks," Bradshaw said. "I think FDA will say that this [Opana review] is not novel and they have always looked at abuse."

REMEDY IS 'AT THE APPROVAL STAGE'

Sid Wolfe, founder and senior adviser to Public Citizen's Health Research Group, took issue with Endo's statement that FDA's withdrawal request does not indicate uncertainty with the product's safety or efficacy when taken as prescribed.

"They are intentionally missing out on the blurred line between using [the drug], getting addicted and then some proportion of those people will wind up abusing the drug," Wolfe said, calling Endo's initial response to FDA's announcement "reckless."

"In proportion to how many people will use and, in many cases abuse the drug … between yesterday's FDA decision and the ultimate, but certain forced removal of the drug, Endo will be exposed to many product liability lawsuits from those damaged or their surviving families," Wolfe said.

While the consumer advocate applauded FDA for seeking the product's withdrawal, he also faulted the agency for approving the reformulation in the first place.

Wolfe pointed to information in FDA's advisory committee briefing book that showed agency concerns during its preapproval review of the new formulation that the extended-release properties could be defeated through certain types of manipulation. He also criticized the agency for failing to seek advisory committee input before approving the reformulated product.

"The remedy for all this is at the approval stage," Wolfe said. The advisory committee meeting in March "came five years and three months after approval and after they'd accumulated a massive amount of epidemiological data" showing an increase in intravenous abuse.

The question of whether a higher regulatory bar for approval is needed will likely be considered by FDA's new Opioid Policy Steering Committee, which Gottlieb has tasked with re-examining the current policy framework for evaluating the risk of abuse and misuse as part of the review process for new opioids. *(Also see "Opioid Policy At US FDA To Become 'More Forceful,' Gottlieb Says" - Pink Sheet, 24 May, 2017.)*

'TIP OF THE ICEBERG'

Bradshaw predicts the agency will become more aggressive in how it views the abuse potential of existing products, particularly given Gottlieb's vows during his confirmation to make responding to the opioid crisis the agency's top priority. *(Also see "Opioid Policy At US FDA: Gottlieb Seeks More Activist Role To Combat Abuse" - Pink Sheet, 7 Apr, 2017.)*

"I think this may be the tip of the iceberg," Bradshaw said of the Opana action. "I think we probably will see the FDA taking additional action against products [and] formulations that can be easily abused, so long as the market is adequately supplied by abuse-deterrent formulations."

"I think the writing is now on the wall that if you have a product that can be abused and there are alternatives to that product that are similarly efficacious, you may soon be coming off the market because of the change now in the safety profile of your drug," he said.

Some Wall Street analysts agree that the Opana action may be a harbinger for stricter regulatory scrutiny.

In a June 8 note, BMO Capital Markets Analyst Gary Nachman called FDA's request for withdrawal "a muscular move, sending a strong statement that FDA will be much tougher regarding opioid

abuse/misuse in this country, and other manufacturers of opioids could be affected down the road as well."

FDA said it could not speculate as to what action it might take in regard to other opioid products.

"The FDA will take steps to remove a drug from the market when the FDA is concerned that a drug's risks now outweigh its benefit," the agency said. "Among other factors, the FDA considers the severity of the condition the product is intended to treat and the benefits and risks of other available therapies for the condition."

Opioids formulations that are more readily manipulated for intravenous injection may be at risk for regulatory action given some advisory committee members' recommendation at the March meeting that FDA should prioritize deterring intravenous use over the less risky intranasal abuse. *(Also see "US FDA Strategy On Abuse-Deterrent Opioids Needs Rethinking, Panelists Say" - Pink Sheet, 15 Mar, 2017.)*

Pernix Therapeutics Holdings Inc.'s *Zohydro ER* (hydrocodone extended-release) also could come in for heightened scrutiny.

FDA's 2013 approval of the product (at that time owned by **Zogenix Inc.**) despite a negative advisory committee review drew sharp criticism from lawmakers, law enforcement officials, public health advocates and advisory committee members themselves. While FDA subsequently approved a new Zohydro ER formulation with physicochemical properties intended to make the drug difficult to crush and dissolve in liquid, the product still lacks abuse-deterrent labeling claim. *(Also see "Zohydro Approval Haunts FDA Panelist At Vantrela Meeting" - Pink Sheet, 13 Jun, 2016.)*

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CONSUMER PRODUCTS

Prestige Brands Updates PediaCare NDC Information A Year After Sale

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The erroneous SPL information was submitted before Prestige Brands acquired the brand in 2010 and was not corrected before firm sold PediaCare and other product lines to Moberg.

Prestige Brands Holdings Inc. is responsible to correct information in FDA's National Drug Code Directory for two products in a line it sold a year ago, the *PediaCare* OTC allergy and cough/cold brand.

The manufacturer and marketer of OTC drugs and personal care products said it will correct the Structured Product Labeling (SPL) information in the NDC Directory for PediaCare *Children's Plus Multi-Symptom Cold* and *Children's Plus Flu* to include an active ingredient in the products, phenylephrine. Both liquid medicines, marketed under an OTC monograph, also contain chlorpheniramine and dextromethorphan.

The products are now marketed by Swedish firm **Moberg Pharma AB** following a deal announced in July 2016, but NDC information in the directory had not yet been updated to reflect that change. Thus, Prestige is responsible to correct the SPL as well as the NDC information.

In a June 1 warning letter, FDA advised Prestige Brands that a review of the products' required listing showed the ingredient is listed on current labeling, but not in the SPL information that also is required for the NDC Directory. NDC owners must update each product's directory listing twice annually, by June and by December.

The warning from the Center for Drug Evaluation and Research stated that FDA removed the products' listing from the online NDC Directory and it will not be available for public viewing until the corrections are made. However, listings for the other products in the PediaCare line

are accurate and remain accessible.

"This is an effort to maintain a correct and accurate database in order to protect and promote the public health," according to the warning letter.

The products will remain available while the NDC Directory information is inaccessible, says Prestige Brands.

Phil Terpolilli, director of investor relations, said the erroneous SPL information was submitted before Prestige Brands acquired the brand in 2010 from **Blacksmith Brands Inc.** and was not corrected before the Tarrytown, N.Y.-based firm sold PediaCare and several other product lines to Moberg. *(Also see "Prestige Brands Makes "Seismic Shift" To OTC With Blacksmith Acquisition" - Pink Sheet, 27 Sep, 2010.)*

In an email, Terpolilli said that corrections are in process and "will include the marketing end date (i.e., the date on which the last batches distributed under our control will expire)."

Blacksmith Brands' NDCs came with the portfolio of products Prestige Brands acquired. "Accordingly, the contact information for that labeler code was updated with FDA, but there was no need to submit new drug listings as a result of the acquisition," Terpolilli said.

In addition to PediaCare, Prestige Brands divested its Fiber Choice and New Skin lines to Moberg for $40m. *(Also see "Moberg Sustains Derma Drive, Acquires Prestige Brands' New Skin" - Pink Sheet, 1 Jul, 2016.)*

In December, Moberg exercised an option gained in the firm's agreement to acquire Prestige Brands' DermoPlast topical anesthetic brand for $47.6m. The Stockholm-based firm, which operates a US business in Cedar Knolls, N.J, since early 2015 has been adding and selling brands with a goal of focusing its business primarily on derma products.

The sales to Moberg were "non-core" brands Prestige Brands is divesting to accelerate paying down debt and move toward its goal of a portfolio with 85% of revenue from "invest for growth" brands and 15% in non-core, or "manage for cash" brands to help support long-term organic growth.

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New Plain Language Labeling Rules Come Into Play For Non-Rx Drugs In Canada

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New plain language labeling requirements for non-prescription drugs came into force in Canada on June 13, introducing new obligations for sponsors to display safety information in a clear and easy-to-understand format.

Sponsors of non-prescription drugs will have to include a new standardized table format on the outer labels of their products, quote mandatory contact information for users to report problems and adverse drug reactions, submit labeling mock-ups for review by Health Canada, and submit evidence that their product's name will not be confused with existing brand names.

Affected products should be in full compliance with the drug facts table requirement at the retail level by June 30, 2021. This is when Health Canada will start verifying compliance, the regulator said in a new guideline issued to help sponsors comply with the new requirements.

The Canadian Drug Facts Table (CDFT) is similar to the nutrition facts table for foods in Canada and the drug facts box required for over-the-counter drugs in the US. It uses simple language and an easy-to-read format to help consumers: compare and choose products; identify the active ingredient(s) and dosage; know what the product is used for; locate warnings and directions for use; identify inactive ingredients that are important to avoid potential allergic reactions; and know how to contact the manufacturer with product questions or concerns

While sponsors of natural health products, such as vitamins and minerals, do not have to comply with plain language labeling regulations, Health Canada is advising them to adopt a facts table, called the "Product Facts" table, on their product labels as a best practice.

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Regarding the requirement for submission of mock-ups, Health Canada clarified that this requirement will not be applied retroactively and that mock-ups will only be needed with submissions that are filed on or after June 13, 2017. Mock-ups will also not be required for submissions in queue for review.

The current requirement to submit final labels after a drug is available for sale has been repealed under the plain language labeling regulations. Therefore, sponsors who file submissions on or after June 13 will not be required to submit final marketed labels with their market notification as labels would be reviewed and finalized prior to approval, Health Canada explained.

The plain language labelling Initiative was launched in 2014 under which new regulations amending the Food and Drug Regulations (Labelling, Packaging and Brand Names of Drugs for Human Use) were issued. *(Also see "'Plain language review' in store for all drug labels in Canada under new regs" - Pink Sheet, 7 Jul, 2014.)* New labeling requirements are already in place for prescription drugs and medicines that are administered or obtained through a health professional.

From the editors of Scrip Regulatory Affairs. Published online June 14, 2017

Sandoz US President Peter Goldschmidt Talks Generic Policy Improvements

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Sandoz Inc. President and Head of North America Peter Goldschmidt said in an interview that the US is behind other markets when it comes to getting complex generics and biosimilars to market and regulatory improvements are needed to speed new hard-to-replicate copies to market.

"There is strong hope the new administration is pushing to get these products faster to market," he said in an interview mainly to discuss the US pressure on the generics market.

A meeting with Health & Human Services Secretary Tom Price and public comments from the new FDA commissioner Scott Gottlieb have left him encouraged, he said.

"There is a clear interest to understand what can be done in order to get faster uptake of complex and differentiated generics," he said. "If you look at the generic *Advair*, biosimilars, but also the other areas, you see the US is behind other regions in terms of getting these to market."

Two applications for the generic versions of **GlaxoSmithKline PLC**'s blockbuster asthma drug Advair (fluticasone/salmeterol) were recently rejected by FDA, from **Mylan NV** and **Hikma Pharmaceuticals PLC**. The delay in this instance is beneficial to Sandoz because the **Novartis AG** generic drug unit is developing its own Advair copy for the US market.

Sandoz submitted a citizen petition to FDA, looking to block other generics, claiming FDA's guidance document on generic Advair lacked certain study requirements, and FDA ultimately hedged in response, denying the petition but without comment, then refusing to approve generics. *(Also see "Advair Generic Approval Uncertain Despite US FDA Denial Of Sandoz Petition" - Pink Sheet, 29 Mar, 2017.)*

On the subject of the citizen petition, Goldschmidt said, "It's difficult to read the FDA on the citizen petition. Our citizen petition shows a clear way for approvability and we have a clear understanding of what we need to do in order to have a very strong development."

Generic versions of Advair have been available in Europe, however, since 2015.

> "The quality will be absolutely key, but I think there is more and more understanding of what needs to happen to save money for the healthcare system," Goldschmidt said. "I think the financial component of a potential generic application will play a role as well."

Gottlieb, meanwhile, has made the issue of smoother generic drug approvals a central component of strategy for running FDA and discussed the issue during his confirmation hearing, claiming that FDA needs to develop better scientific principles to assure bioequivalence of more complex drugs. *(Also see "Complex Generics: Gottlieb Eyes FDA Policy Changes To Speed Approvals" - Pink Sheet, 6 Apr, 2017.)*

Accomplishing this is not just about more resources, Goldschmidt said. Generic drug manufacturers would like to see more guidance documents for complex generics and biosimilars to smooth the development path.

"Molecule specific or [active pharmaceutical ingredient] specific," Goldschmidt said. "Sometimes, not only is it the molecule, but sometimes it is exactly what needs to be done to see if the API is fully interchangeable."

Prioritizing high-priority ANDAs is another opportunity to bring new generics to market faster. On this issue, Goldschmidt said the system appears to be moving in that direction, driven largely by the need to reduce drug costs.

"The quality will be absolutely key, but I think there is more and more understanding of what needs to happen to save money for the healthcare system," he said. "I think the financial component of a potential generic application will play a role as well."

Generic drug manufacturers are looking increasingly to complex generics and biosimilars to drive growth as challenges persist in the traditional small molecule generic sector, including steep price erosion driven by customer consolidation and FDA's efforts over the last three years to reduce the enormous ANDA backlog *(Also see "ANDA Stress Test: End-Of-Year Submission Bolus Pressures US FDA Review System" - Pink Sheet, 9 Jan, 2017.)*. The challenging market conditions in the US are expected to continue through 2017.

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India To Streamline Tiered Trial Approval Process – Will It Lift Sponsor Outlook?

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> "This will overall augur well for clinical research in India" – Naz Haji, QuintilesIMS India

A key panel of government functionaries has stipulated plans to revamp the three-tier approach for clinical trial approvals in India, bringing significant relief to the beleaguered clinical research sector in the country.

India currently follows a layered review process for clinical trial-related approvals, under which applications are initially evaluated by specialized Subject Expert Committees (SECs), whose recommendations are then generally vetted by a Technical Review Committee and finally cleared by the Apex Committee.

The new approach appears to do away with the mandatory multi-layer approval approach for the most part. Significant power appears to be vested in the hands of the SECs in deciding on approvals of proposals for global clinical trials (GCT) in India – once proposals are accepted or rejected by the SEC, no further approval of the Technical Committee Or Apex Committee will be required.

"In cases, where the DCGI [Drugs Controller General of India] is not in agreement with the recommendations of SECs in case of clinical trial application, the matter may be placed before the Technical Committee for a final decision within a month of the recommendations of the SEC," it was decided recently at a meeting of the Apex Committee chaired by the C K Mishra, secretary, department of health and family welfare, ministry of health and family welfare.

The Apex Committee noted that it "had been apprised that the system of examination of [clinical trial] proposals in CDSCO [Central Drugs Standard Control Organization] has since reached a maturity and, therefore, it will be appropriate that the approval processes should be streamlined."

PROCESSES STREAMLINED

The Apex Committee, at its meeting on June 2, held that cases, where a clinical trial applicant is "aggrieved" by the SEC's rejection of its proposal, are to be placed before the Technical Committee for its consideration.

"Where the Technical Committee decides, for reasons to be recorded in writing, to over-rule the SEC, the decision of the Technical Committee shall be final," details in the minutes of the Apex Committee meeting said.

The Apex committee also noted that IND [investigational new drug] clinical trial applications shall be placed before the IND Committee, and the decision of the IND Committee shall be final.

"DGHS [Director General of Health Services] or Special DGHS may be invited to the meetings of the IND Committee. In rare cases, where the IND Committee considers it necessary to keep the Apex Committee informed, the matter may be placed before the Apex Committee for guidance," the meeting minutes added.

The Apex Committee also said that a summary of the applications received, proposals pending/rejected, clarifications sought, and approved at different levels would need to be submitted for its perusal every month.

"Central Drugs Standard Control Organization will, in consultation with C-DAC [Centre for Development Advanced Computing], examine whether the report can be generated through SUGAM [the online portal]," it added.

TIMELINES CLOSER TO THOSE OF DEVELOPED MARKETS

Industry welcomed the latest tweaks, suggesting that the streamlining will help to significantly shorten approval timelines, while ensuring a "high degree of scrutiny" by regulators before approval.

Naz Haji, senior vice president and managing director, QuintilesIMS India, told the *Pink Sheet* that while approval timelines had reduced significantly in the last couple of years and were averaging around six to seven months, there was scope to further reduce these to ensure faster access to treatment for patients.

"With the regulatory authorities now addressing this without compromising on patient safety and well-being, we will soon have more competitive approval timelines and an 'India advantage' sponsors would welcome, which in turn would benefit patients. This will overall augur well for clinical research in India," Haji said.

The Indian Society for Clinical Research, whose members include several large multinational firms and clinical research organizations, indicated that with approval timelines likely to be "closer to those of many developed markets", India will have a competitive edge which will boost global drug development in India as it can participate in more global trials.

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"This will help provide faster access of drugs to our patients (post successful completion of the trials) and better address our unmet medical needs," ISCR President, Chirag Trivedi, said.

The ISCR also believes the tweaks will encourage domestic companies, many of whom had moved their trials outside India due to delayed approval timelines, to do more studies in India and help "Make in India" a reality for drug research and development. India's Prime Minister Narendra Modi had, in 2014, launched the "Make in India" initiative, that essentially aims to make India a global manufacturing hub, thereby upping the contribution of the manufacturing sector to the country's gross domestic product (GDP).

TOO MUCH LATITUDE?

But does the streamlined trial clearance plan give too much latitude to SECs, known, by industry's own admission, to have a less-structured approach in deciding on trial approvals?

ISCR's Trivedi told the *Pink Sheet* that the Indian regulator had recently released a handbook in which clear instructions have been provided to the SECs for reviewing clinical trials. The handbook provides detailed steps for review by the SEC.

"We believe the SECs have more clarity on the requisite guidelines for reviewing clinical trials. Moreover, the Apex Committee decision clearly stipulates that if the DCGI does not agree with the SEC's decision, then the matter will be referred to the Technical Committee. Hence, there are enough checks and balances built into the review and approval process," he explained.

The functioning of the SECs, at least in the past, has been a significant pain point for trial applicants.

Industry experts had earlier claimed that the SEC experts do not really know certain regulatory aspects very well and noted how invariably "one or two very vocal experts carry the discussion the way they want".

India has, over the recent past, unveiled several regulatory tweaks in the clinical trial segment as it seeks to remove bottlenecks alongside balancing its intent to promote "scientific and ethical clinical trials" in the country. *(Also see "India Eases Approval Process For HIV, Hepatitis Combinations" - Pink Sheet, 24 Mar, 2017.)*

Last year, Informa's Trialtrove noted how the "rosy view" of India as a location for relatively low-cost clinical trials with a readily available, treatment-naïve patient population became shaded over the past five years by an untenable time to approval. India's clinical research sector has, in general, been dented amid uncertainties and delays caused by evolving regulations and ongoing trial-related litigation among other factors. Compliance issues pertaining to a few local CROs have only compounded problems for the rest of industry.

From the editors of PharmAsia News. Published online June 9, 2017

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Novo Nordisk's *Victoza* (liraglutide) as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse CV events in adults with type 2 diabetes and high CV risk	Endocrinologic and Metabolic Drugs	June 20
Potential pediatric development plans for Apexigen's APX-005M, PharmaMar USA Inc.'s PMO1183 (lurbinectedin) and Astellas Pharma Global Development's ASP2215 (gilteritinib)	Pediatric Oncology Subcommittee	June 21
Potential pediatric development plans for Dista Products/Eli Lilly's prexasertib and Lilly's olaratumab	Pediatric Oncology Subcommittee	June 22
FDA biotechnology activities related to plant-derived food and animals and report from the National Antibiotic Resistance Monitoring System Review Subcommittee	Science Board	June 26
Pfizer's *Mylotarg* (gemtuzumab ozogamicin) in combination therapy with daunorubicin and cytarabine for the treatment of adults with previously untreated, de novo acute myeloid leukemia	Oncologic Drugs	July 11
Novartis' tisagenlecleucel-T suspension for treatment of pediatric and young adults ages 3-25 years with relapsed/refractory B-cell acute lymphoblastic leukemia	Oncologic Drugs	July 12
Amgen's ABP 215, a proposed biosimilar to Genentech/Roche's *Avastin* (bevacizumab)	Oncologic Drugs	July 13 (morning)
Mylan's MYL-1401O, a proposed biosimilar to Genentech's *Herceptin* (trastuzumab)	Oncologic Drugs	July 13 (afternoon)
Safety and efficacy of Dynavax's hepatitis B vaccine	Vaccines and Related Biological Products	July 28

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