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# Feel The Quality: Biosimilars Dominate Standards Setting Debate In EU

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A number of quality issues have emerged from the scientific advice procedures that have been held so far to discuss marketing authorization applications to the European Medicines Agency for biosimilar medicines, such as the use of statistical methodology in comparing quality attributes, a greater focus on efficient and robust quality datasets, and the use of a non-EU comparator drug.

Peter Richardson, head of quality at the EMA, explored these and other questions at a recent seminar where delegates discussed the respective roles of the agency and the European Pharmacopoeia (PhEur) in the biological/biosimilar regulatory framework and how PhEur monographs are applied in assessing the quality of biosimilars.

The event, which took place on Feb. 8 at the EDQM's Strasbourg headquarters in France, was organized by the agency and the European Department for the Quality of Medicines and Healthcare (EDQM), which publishes PhEur monographs.

Looking at the quality issues involved in the comparability exercise that forms the core of the biosimilar evaluation procedure at the EMA, Richardson said that quality aspects were "really the foundation of the dossier" for a biosimilar application, on which "we base a lot of decision-making." Biosimilars require "state-of-the-art" characterization and "quality is the key."

Quality "looks very carefully at structures, looking for any differences and trying to understand them" and determining how relevant they are, Richardson said. While there will always be some differences in quality between the biosimilar and the reference drug, these may need justification. "If the quality attributes deviate, we get the company to give us more data for reassurance."

He said a number of quality issues were currently being discussed in light of past scientific advice sessions conducted between the EMA and biosimilar applicants.

Among them was the need to focus on ensuring efficient and robust quality datasets and look at how far quality data can reduce the need for non-clinical and clinical data on a biosimilar. As thinking on biosimilars has evolved, the aim is increasingly "to show biosimilarity, not to re-demonstrate safety and efficacy," Richardson said.

He also noted that biosimilar scientific advice requests increasingly include a discussion on statistical methodology for quality aspects, and so a reflection paper on how to apply statistics to determining a product's quality attributes is being developed, on the basis of a concept paper published in 2013. The paper may cover biosimilar development and comparability evaluation and discuss relevant methodologies, he observed.

The EMA will also be offering tailored scientific advice for some biosimilars as part

CONTINUED ON PAGE 4

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13


16

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of a pilot scheme due to begin this month. *(Also see "Biosimilars Get Bespoke Service: EMA To Pilot Tailored Scientific Advice" - Pink Sheet, 28 Dec, 2016.)*

Turning to the role of pharmacopoeial monographs, Richardson said that they provide the "minimum quality standard" for medicinal products, give guidance on limits for critical attributes, and "facilitate convergence on robust validated methods" of assessing quality aspects.

But in the case of biologicals, which are more complex and heterogeneous than chemical drugs, monographs should be flexible and "should not be a development checklist," he said.

## NEED FOR FLEXIBILITY

The need for flexibility in biological monographs was also raised by Emmanuelle Charton of the European Pharmacopoeia Department at the EDQM. Noting that the PhEur is legally binding and lays down "common, compulsory quality standards" for all medicinal products in Europe, she said that setting public standards for biological medicines was a "complex and challenging exercise."

The challenge, she said, lay in finding an appropriate balance between having enough flexibility so that the monographs can apply to a wide range of products, and the need to have sufficiently prescriptive quality requirements to allow analytical procedures to be carried out successfully in a control lab. "Too much flexibility leads to a meaningless standard," Charton declared.

She said the European Pharmacopoeia provided the legal requirements for quality (i.e., the specifications), "but on other hand it has to keep up with current thinking and concepts so flexibility is needed – can a monograph be both a suitable public standard and flexible?" she asked. "The answer is yes."

Practical steps are already being taken towards finding this balance. The EDQM recently reported the results of a pilot study on biotherapeutic monographs that showed "robust" but flexible quality standards could be established for complex molecules and used in the development of biosimilars as more originator products lose patent protection. *(Also see "New European Monographs Set 'Robust Standards' For Biosimilar Development" - Pink Sheet, 11 Jan, 2017.)* The monographs covered insulin glargine, rDNA Factor VIIa, rDNAFactor IX, teriparatide, and etanercept.

> Both Richardson and Charton went out of their way to stress that monographs do not constitute regulatory standards for the demonstration of biosimilarity for drug approval purposes.

Both Richardson and Charton went out of their way to stress that monographs do not constitute regulatory standards for the demonstration of biosimilarity for drug approval purposes – i.e., they cannot replace the comprehensive comparability exercise between the biosimilar and its reference product. There have been reports that some "less stringent" regulatory authorities have been using monographs to approve biosimilars – an issue that was brought up at the PhEur conference late last year. *(Also see "Poor Biosimilarity Practices, Impurities and New Technologies Debated At European Pharmacopoeia Event" - Pink Sheet, 6 Oct, 2016.)*

As more biologicals reach the end of their patent life, the processes of elaborating a biological monograph and approving a biosimilar are increasingly taking place more or less simultaneously. This was the case, for example, with insulin glargine and follitropin, and more recently with biosimilar etanercept, which was approved for marketing in 2016 around the same time as the respective monograph was published, Charton observed.

## NON-EU COMPARATOR

A number of issues arose in the question and answer session at the seminar, including the question of global biosimilar development – i.e., using a non-EU-approved reference drug as the comparator. This is allowed by EU guidelines under certain circumstances – for example the comparator must be authorized by a regulatory body with similar scientific and regulatory standards to the EMA, and must be representative of the reference product (to be shown via bridging data).

Richardson said the EMA had been liaising closely with the US Food and Drug Administration, which was "in some ways the primary target because of the number of biosimilars that are going into the US market." Facilitating international convergence on this was a priority, he said, "and we now mutually accept studies performed in each other's jurisdiction for the clinical data."

For companies in Europe proposing to use a non-EU comparator, Richardson said that "if anyone is trying to do this, come and speak with the regulatory authorities first for their perspective on which jurisdiction they would be proposing as the source and where the clinical trials are coming from." He said the arrangement was "fully functioning with our US colleagues and it could be pushed further in the near future."

The global development issue also cropped up when a delegate asked what might happen where the originator drug had been withdrawn from the market, for example in Europe.

Richardson said that for a biosimilar product "you need a direct comparison" of the two. If the reference drug was available in another jurisdiction, "there could be a mechanism by which that could be used under the global development approach. If it was not on the market anymore, we would need to think of a workaround – there would still be value in the data that was available, but how to reinvigorate it would be a challenge."

The question of ensuring that monographs remain suitable for biologicals in the future is currently the subject of a public consultation being run by the UK Medicines and Healthcare products Regulatory Agency. *(Also see "Biological Quality In The Spotlight As UK MHRA Consults On Standard-Setting" - Pink Sheet, 15 Feb, 2017.)*

*From the editors of Scrip Regulatory Affairs. Published online February 20, 2017*

# 'Non-Medical Switching' Claim Riles Europe's Biosimilars Industry

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Despite growing support for the use of biosimilar medicines in Europe, two patient advocacy organizations have again raised concerns over issues like traceability, informed patient consent and what they call "non-medical switching" – i.e., switching for economic rather than clinical reasons.

In a recently published report, the Global Alliance for Patient Access (GAfPA) and the European Federation of Crohn's & Ulcerative Colitis Associations (EFCCA) – both of which receive funding from a range of multinational pharmaceutical companies – claim that there is much still to be done to allay patients' concerns over the safety profile of biosimilars and the long-term effects of switching patients from an originator drug to a biosimilar version.

But the association representing European generic and biosimilar companies, Medicines for Europe, has hit out at the report, saying that the concept of "non-medical switching" is an "invented term" that will "simply cause confusion for patients," and that there is already a groundswell of opinion among European regulators and medical associations in favor of biosimilar switching.

The GAfPA/EFCCA report is based on a November 2016 conference held at the European Parliament offices in Brussels that the organizations say was attended by patient and physician advocates "from almost every country in the EU," representing a variety of autoimmune conditions and the fields of gastroenterology, rheumatology, and dermatology. The aim was to "explore the topic of biologics and biosimilars and how different policies and practices across Europe impact on patients."

Among the concerns raised at the conference were low awareness of biosimilars among patients, the lack of data on multiple switching, the appropriateness of extrapolation of indications, and claims that some patients are given biosimilars "without their knowledge or consent."

To support the low awareness claim, the results of a 14-question online survey of 1,181 respondents with inflammatory bowel disease (IBD), conducted by EFCCA between November 2014 and October 2015, were presented at the meeting. 56% of the respondents had Crohn's disease, and 34% ulcerative colitis. Most of them came from Europe, and were generally 21-50 years old. 48% were currently being treated with biologicals, while 42% had never been exposed to such drugs.

Among other things, the survey found that 62% of the patients had not heard of biosimilars, and of those who had, "the majority expressed concern about their safety profile," the report said. "Patients had a clear desire to be involved in decisions about their treatment, with 43% stating that patients should be given information about their treatment. 27% said that they would accept switching on the basis of evidence-based data."

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## "NON-MEDICAL SWITCHING"

At the conference, Dr Alessandro Armuzzi, head of the IBD Unit at the Catholic University of Rome, gave "an overview of the differences between biologic and biosimilar medicines," saying that these differences required biologic and biosimilar medicines to be "approved in different ways."

Armuzzi observed said that some healthcare systems across the EU had "encouraged the practice of non-medical switching," and that while a single switch from a biologic to a biosimilar medicine – "in which the patient is fully informed about the change in medication – may be appropriate," there was "not enough data on a number of switches, or switching between biosimilar products, for these practices to become established." He added that the long-term effects of "non-medical switching" on patients were yet to be seen.

The meeting also discussed the results of the Norwegian NOR-SWITCH study involving switching from Janssen's Remicade to Celltrion's biosimilar infliximab, Remsima, over which the originator and biosimilars industry have already clashed. *(Also see "NOR-SWITCH Results 'Concerning' In Crohn's Disease, Says Janssen" - Pink Sheet, 11 Nov, 2016.)*

David Charles, chair of GAfPA's Biologics and Biosimilars Working

Group, was cited in the report as saying that while NOR-SWITCH showed biosimilar infliximab was not inferior to Remicade, it was applicable only to these two specific products, it pooled data rather than separating it by individual disease state, and it did not take account of the effects of multiple switches.

Charles also raised "the importance of being able to track and trace biosimilar medicines to record any adverse reactions to a particular treatment." The meeting heard that "underreporting of adverse reactions was a challenge" with biologic medicines, and that national pharmacovigilance systems varied in their effectiveness. Non-serious reactions, or recurrent reactions, were "rarely reported", and when they were, they were "often of poor quality, missing batch numbers, brand names or patient information."

## "NEW AND INVENTED TERM"

Medicines for Europe gave the report short shrift. Its director general, Adrian van den Hoven, told the *Pink Sheet* that "non-medical switching" was a "completely new and invented term that has nothing to do with science or medical practice or even policymaking for medicines."

A switch is by definition a medical act, i.e., one involving a clinical decision maker, van den Hoven said. "The term 'non-medical' switching has recently been invented and its dissemination contributes to a high level of confusion among patients and physician communities."

The medical practice of switching a medicine for another one with the same therapeutic intent (the European Commission definition) is not only common but is broadly supported, not only by national authorities in Europe but also by the muscular and rheumatic disease body EULAR, the European Society for Medical Oncology (ESMO) and the European Crohn's and Colitis Organisation ECCO, which have all taken positions to this effect, he said. *(Also see "Biosimilars Boost In Europe: 2017 Kicks Off With Three Approvals And Backing From ESMO" - Pink Sheet, 24 Jan, 2017.)*

As well as the NOR-SWITCH study, many other smaller European switching studies have shown positive results. "The reality is that the theory, the switching studies and the real world experience in Europe all confirm biosimilarity," van den Hoven noted.

As for traceability, van den Hoven said this was not an issue in Europe, where there was "over 95% brand name identification within pharmacovigilance adverse event reporting as per preliminary results of an EMA [European Medicines Agency] study to be published in Q2 2017." He conceded that batch number recording remained an issue for all biologic medicines, particularly within the hospital setting, saying it was "of utmost importance to foster enhanced recording."

The Medicines for Europe director also noted that GAfPA is a US-based organization and that the "people who have presented on their behalf are all American," and said the relative lack of experience with biosimilars in the US "may explain some of their views." However, "they should learn about the EU experience, data and science if they want to present seriously about biosimilar medicines to patients," he declared.

The report's publication coincided with the disclosure of results from a randomized controlled trial (RCT) with Celltrion's Remsima (CT-P13), which the company says showed that its safety and efficacy were comparable to those of the originator drug, Janssen's Remicade, in patients with Crohn's disease (CD).

The double-blind, parallel-group Phase III study was designed to investigate the efficacy and safety of Remsima and Remicade in CD patients, as determined by the Crohn's Disease Activity Index (CDAI). According to the six-week and 30-week data, similar clinical remission, CDAI-70 and CDAI-100 response rates were observed in both the Remsima and Remicade groups.

> Medicines for Europe's van den Hoven said "non-medical switching" was a "completely new and invented term that has nothing to do with science or medical practice or even policymaking for medicines."

Jørgen Jahnsen, professor of gastroenterology at the University of Oslo, Norway, said this was the first RCT to examine the use of a biosimilar in inflammatory bowel disease. "While we already have a wealth of extrapolated and real-world data for CT-P13, gastroenterologists have for some time wanted the reassurance of an RCT and it's encouraging to see such positive data from Celltrion's RCT trial."

Celltrion also presented data from two observational studies. The first evaluated the efficacy and safety of Remsima in 74 pediatric patients with CD (26 naive patients, and 25 switch patients) or ulcerative colitis (16 naive patients, seven switch patients). The data showed that Remsima was effective in both treatment-naive and switch pediatric patients over 30 weeks and was well tolerated, the company said.

The second study examined 204 CD patients in South Korea from July 2012 to 2016. Remsima was found to be clinically consistent to reference infliximab and well tolerated up to six months in patients with moderate-to-severe CD and those with fistulizing CD.

Celltrion added that in the 18 months from January 2015 to mid-2016, real-world cost savings with Remsima in all its indications were €32.4m across Germany, Italy, Spain and the UK.

## TRUXIMA EU APPROVAL

Separately, Celltrion announced Feb. 22 that its biosimilar product Truxima, a version of Roche's *MabThera* (rituximab), had been authorized for marketing in the EU, following a positive opinion from the European Medicines Agency in December 2016. Truxima is the first biosimilar anticancer to receive a marketing authorization in Europe.

*From the editors of Scrip Regulatory Affairs. Published online February 22, 2017*

# How To Name A Biosimilar: Amgen Persisted With Amjevita Suffix Despite FDA Doubts

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**Amgen Inc.**'s experience with *Amjevita* (adalimumab-atto) could serve as a case study for other biologic product sponsors hoping to get their preferred distinguishable suffix through the US FDA's new nonproprietary name review process.

FDA initially rejected the company's preferred suffix, "-atto," for its biosimilar to **AbbVie Inc.**'s TNF-inhibitor *Humira* (adalimumab) because it contained common medical abbreviations that, the agency believed, may present a risk for errors. The proposed suffix also was the subject of live trademarks at the US Patent and Trademark Office (PTO).

Amgen persisted, however, and submitted analyses and justification supporting its view that "-atto" would not be confused with other medical abbreviations and the trademark issue was not a concern.

FDA ultimately accepted these arguments, finding it unlikely both that a subset of letters within the suffix would be misread as a standalone medicine and that any overlap with medical abbreviations would lead to errors. The agency also was sufficiently convinced that the suffix would not create confusion with several registered trademarks.

In review documents, the agency makes clear it is looking for data-driven arguments from sponsors as to why a preferred suffix does not raise regulatory red flags.

The example offers a peek into how FDA will apply the factors governing acceptable and unacceptable suffixes described in a recent final guidance document on nonproprietary naming of biologic products. Notably, the suffixes for both adalimumab-atto and the biosimilar that immediately preceded it, **Sandoz Inc.**'s *Erelzi* (etanercept-szzs), got tripped up by FDA's concern that they could be confused with medical abbreviations. *(Also see "Sandoz Tested Erelzi's Suffix On Multiple Fronts" - Pink Sheet, 20 Feb, 2017.)*


Sponsors of biosimilars and novel biologics alike need to get on top of the suffix issue early and have numerous alternatives lined up for agency review.

## SUFFIX DEVELOPMENT: EARLY AND OFTEN

The Amjevita experience also highlights the need for sponsors of biosimilars and new biologic products alike to get on top of the suffix issue early and have numerous alternatives lined up, particularly now that FDA has finalized its guidance on nonproprietary naming.

At the time of Amgen's BLA submission, FDA's existing guidance recommended sponsors submit up to three suffixes. In final guidance released in January, the agency increased that number to 10 and provided more clarity as to when suffixes should be submitted. *(Also see "Biological Product Suffix Submissions Limited To 10 Candidates By US FDA" - Pink Sheet, 16 Jan, 2017.)*

Amgen's experience shows the importance of having numerous suffix proposals internally vetted and ready for regulatory consideration, particularly given the ticking user fee clock on product reviews.

Suffix reviews are still a fairly new undertaking at FDA and the nonproprietary name approvals for both Amjevita and Erelzi came very close to the products' user fee goal dates. In fact, the suffix review process does not appear to have started until late in the BLA review cycle for both products.

## ON HEELS OF DRAFT NAMING GUIDANCE

FDA licensed Amjevita (formerly known as ABP 501) on Sept. 23 for seven of the indications on Humira's label. *(Also see "Amgen's Amjevita Approved As First Biosimilar To AbbVie's Humira" - Pink Sheet, 23 Sep, 2016.)* Pursuant to FDA's August 2015 draft guidance on nonproprietary naming of biologics, Amjevita became the third biosimilar with a four-letter suffix devoid of meaning.

The draft guidance called for distinguishable suffixes devoid of meaning be included in the nonproprietary name of current and future biological products and biosimilars. However, the agency also sought public comments on the use of meaningful suffixes derived from a license holder's name.

In the final guidance document released Jan. 12, FDA stuck with nonmeaningful suffixes for all biologics despite strong support among public commenters for more meaningful and memorable suffixes. The final document included several new factors for sponsors to consider in proposing suffixes, including that they be free of legal barriers that would restrict usage and not look similar to the license holder's name. *(Also see "Biologic Product Naming: US FDA Sticks With Suffixes 'Devoid Of Meaning'" - Pink Sheet, 12 Jan, 2017.)*

In a Jan. 19 response to several citizen petitions, FDA said it opted against a naming system in which the suffix is derived from a license holder's name due to potential confusion if a product's ownership

changes. The agency also noted that suffixes devoid of meaning were "potentially compatible" with the World Health Organization's biological qualifier proposal. *(Also see "FDA Claims Sole Authority Over Naming Of US-Licensed Biologics" - Pink Sheet, 2 Feb, 2017.)*

Several stakeholders have requested the Office of Management and Budget delay implementation of the suffix-based naming policy pending a more thorough analysis of the financial impacts across the healthcare system. *(Also see "FDA's Burden Estimate On Biologic Naming Ignores Downstream Costs, Critics Say" - Pink Sheet, 16 Feb, 2017.)*

## EARLY SUFFIXES DEEMED NON-VIABLE

FDA's preference for nonmeaningful suffixes notwithstanding, Amgen initially tried to go in a different direction with the nonproprietary name for its biosimilar to Humira.

Amgen submitted its biologics license application (BLA) in November 2015, three months after the draft guidance on naming was released. The BLA included proposed nonproprietary name suffixes that were derived from the company's name, according to FDA review documents. *(See reviewers sidebar)*.

Read the full article here

In a July 18, 2016 letter, Kellie Taylor, deputy director of the Office of Medication Error Prevention and Risk Management, requested Amgen submit by July 30 three proposed suffixes, listed in order of preference, comprising four lower-case letters. The suffixes should be devoid of meaning and follow the recommendations in the August 2015 draft guidance, Taylor said.

Taylor said the agency would evaluate the originally proposed suffixes derived from the company's name "in parallel to any suffixes you propose that are devoid of meaning."

FDA had similarly asked **Celltrion Inc.** to suggest three suffixes devoid of meaning when it resubmitted its BLA for *Inflectra* (infliximab-dyyb), a biosimilar to **Janssen Biotech Inc.**'s *Remicade* (infliximab). However, the agency also allowed Celltrion to submit three meaningful suffixes. *(Also see "Biosimilar Naming: FDA Asked Celltrion For Two Kinds Of Suffixes" - Pink Sheet, 15 Jul, 2016.)*

Two weeks before the user fee goal date, Amgen had no other suffix candidates ready for FDA consideration beyond those the agency already deemed problematic.

### MEDICAL ABBREVIATIONS WITHIN "-ATTO"

**"att"** – Anti-tetanus toxoid

**"at"** – Antithrombin

**"tt"** – Tetanus toxoid

**"to"** – Tincture of opium

Following Amgen's submission and the company's follow-up email, FDA requested a teleconference to discuss a path forward on nonproprietary naming. During that teleconference, held Aug. 10, FDA said it had identified concerns with Amgen's proposed suffixes that rendered them non-viable.

Although the proposed suffixes are redacted from FDA's publicly available review documents, the reasons for their rejection are disclosed. Suffixes were rejected for not being devoid of meaning and looking similar to, or being mistaken for, the name of an active NDA.

Additionally, two suffixes returned live trademarks from the US PTO. "If FDA were to proceed further in evaluations we would ask that Amgen conduct due diligence on the proposed suffixes to ensure that no other restrictions apply to the proposed suffix's use in the context of the nonproprietary name," FDA meeting minutes state.

"FDA affirmed that we are eager to work with Amgen given the rapid approach of the goal date for their pending 351(k) BLA," the minutes state. FDA requested Amgen submit additional nonmeaningful suffixes for consideration as soon as possible.

In an Aug. 12 submission, Amgen proposed three suffixes, with "-atto" topping the preference list. However, FDA again raised concerns about all three suffixes in a Sept. 7 letter.

The agency deemed "-atto" unacceptable because it included several common medical abbreviations and may present the risk of errors due to such inclusions. *(See box)* Amgen's second and third preferred suffixes also were deemed unacceptable for including common medical abbreviations.

FDA again raised concerns about trademark issues. "The suffix 'atto' returned live trademarks from USPTO," the agency said. "Please ensure that no trademark or other restrictions apply to the proposed suffixes that you submit for our evaluation in the context of your nonproprietary name."

FDA requested Amgen submit either additional information or data that might address the agency's concerns on the proposed suffixes, or provide additional nonmeaningful suffixes for review.

## FDA WANTS 'DATA-DRIVEN ARGUMENT'

The agency and company had another conference call on the suffix issue Sept. 8, during which Amgen said its analyses suggested the issues with medical abbreviations would be unlikely to result in errors.

"Amgen offered to provide this to FDA for their consideration," the minutes state. "FDA inquired if Amgen had conducted practitioner surveys of the suffix, and Amgen indicated they had not done so but had conducted other relevant searches and analyses. FDA stated that a data-driven argument would be most compelling but that we would review any information provided by Amgen to support their suffix candidates."

FDA also reminded Amgen that it had identified a potential trademark issue with the "-atto" suffix. "Amgen indicated their

own legal analysis failed to identify this issue and that they would provide that to us for our review and consideration," the minutes state.

The minutes reflect the growing sense of urgency about the suffix issue given that the Sept. 25 user fee goal date was a little over two weeks away.

"Amgen further confirmed that they had no additional suffix candidates to submit at this time beyond the original candidates proposed," the minutes state. "Amgen agreed to provide additional information as quickly as possible, and FDA indicated they would work quickly in their review and keep Amgen apprised of the findings and timelines for review completion."

## AMGEN'S JUSTIFICATION PROVES PERSUASIVE

On Sept. 13, Amgen submitted a reconsideration request for the previously proposed suffixes with analyses to address FDA's concerns, and this additional justification proved to be enough to convince FDA. The "-atto" suffix finally found favor with FDA just 10 days before the biosimilar's user fee goal date. *(See timeline, p. 10)*

A memo by Division of Medication Error Prevention and Analysis (DMEPA) reviewer Carlos Mena-Grillasca outlines Amgen's arguments in response to FDA concerns about the "-atto" suffix.

Amgen asserted any analysis of whether a suffix includes common medical abbreviations that could lead to medical errors should be based upon the complete, four-letter suffix and not a portion thereof.

"Amgen believes it is not reasonable to assume that a subset of the suffix would be read as a stand-alone medicine," the memo states. "They argue that if that was the standard of evaluation, then the root names and trade names that include a pair of letters that constitute a meaningful abbreviation would be unacceptable as presenting excessive risk of medication error."

In response, Mena-Grillasca said that given the abbreviations identified within Amgen's proposed suffix, DMEPA agreed "that it is unlikely that a subset of letters within the -atto suffix would be misread as a stand-alone medicine when considering the expected use of this product."

Amgen also argued that most of FDA's identified concerns are based on similarities between two-letter subsets of the suffix from a large database of medical abbreviations. For such similarities to result in a medication error, all of the following would need to occur:

- Only two letters of the suffix of the complete proper name would be read, recognized, or recalled; and
- These two letters would be misinterpreted to mean another product; and
- This would lead to administration of a drug other than Amgen's biosimilar.

Amgen asserted the risk of the first two conditions is no greater than the risk of subsets of letters within a proprietary name that overlap with medical abbreviations, Mena-Grillasca noted. With regard to the latter condition, "Amgen argues that is critical to consider the plausibility of a medical intervention occurring as a result of the potential misreading or misinterpretation of the proper name."

"Of note is the fact that Amgen 'understands' that certain suffixes or subsets could be found unacceptable if it constituted a conflict with a medical term implying potential treatment with adalimumab such as -mtx or -qbd, that could potentially be misinterpreted to mean a particular use of the product," the review states.

Mena-Grillasca said DMEPA "considered the failure modes and effects analysis presented by Amgen regarding the potential for subsets in -atto to lead to confusion, and concluded that the overlap of two-letter or three-letter subsets of -atto with the medical abbreviations FDA previously identified is unlikely to be a source of error for ABP 501."

## CONFUSION WITH TRADEMARKS UNLIKELY

Turning to FDA's concern about registered trademarks, Amgen said the goods in the trademark registrations are not the kind that would be prescribed by medical professionals or distributed in pharmacies. Therefore, there would be no risk of medical error or mistaken prescription.

"DMEPA notes that Amgen has evaluated registered trademarks for potential conflicts and provided justification for why the suffix 'atto' would not create confusion," Mena-Grillasca concluded.

"Based on our analysis of the information submitted by the applicant in support of

## *Amjevita* FDA Reviewers

| | REVIEWERS |
|---|---|
| **Medical** | Keith Hull (Division of Pulmonary, Allergy and Rheumatology Products); Denise Cook (Division of Dermatology and Dental Products); Aisha Johnson (Division of Gastroenterology and Inborn Errors Products) |
| **Chemistry** | Jun Park; Bo Chi (drug substance); Lakshmi Narasimhan (drug product); Steven Fong (facilities) |
| **Clinical Pharmacology** | Jianmeng Chen |
| **Immunogenicity** | Jun Park; William Hallett |
| **Nonproprietary Name Suffix** | Carlos Mena-Grillasca |
| **Pharmacology/Toxicology** | Carol Galvis |
| **Statistics** | Yongman Kim; Kathleen Fritsch; Meiyu Shen (CMC) |
| **Cross-Discipline Team Leader** | Nikolay Nikolov |
| **Regulatory Project Manager** | Sadaf Nabavian |

the nonproprietary name reconsideration request for -atto, we conclude that the proposed suffix is acceptable for ABP 501," Mena-Grillasca said. "We have reconsidered the safety concerns outlined in our previous assessment and find that the information and analysis provided by Amgen allays our concerns with the -atto suffix."

In a statement to the Pink Sheet, Amgen said it "supported designating a distinguishable nonproprietary name via a unique, four-letter suffix. The suffix of -atto is consistent with FDA's guidance and is devoid of meaning." The company declined to provide specifics about other proposed suffixes that were rejected by FDA.

*Published online February 20, 2017*

## *Amjevita* Clinical Development Timeline

| DATE | ACTION |
|---|---|
| **Pre-IND and IND Chronology (#111714)** | |
| 8/24/2011 | Pre-IND meeting |
| 4/2012 | Biosimilar Biological Product Development (BPD) Type 2 meeting on analytical similarity assessment |
| 11/2012 | BPD Type 2 meeting on analytical similarity assessment |
| 5/9/2013 | BPD Type 2 meeting on design of Study 262, a comparative clinical trial in rheumatoid arthritis |
| 1/29/2014 | BPD Type 2 meeting on device aspects for the modified *SureClick* autoinjector |
| 7/2014 | BPD Type 2 meeting on analytical similarity acceptance criteria |
| 1/26/2015 | BPD Type 2 meeting on proposed structure and format of statistical data to be presented in BLA |
| 6/10/2015 | BPD Type 4 meeting on structure, format and content of proposed BLA |
| 8/27/2015 | FDA draft guidance on nonproprietary naming of biological products |
| **BLA Chronology (#761024)** | |
| 11/25/2015 | 351(k) BLA submitted; proprietary name request also seeks review of proposed nonproprietary name suffixes that are derived from the sponsor's name |
| 7/12/2016 | Arthritis Advisory Committee meeting |
| 7/18/2016 | FDA requests Amgen submit three proposed suffixes that are devoid of meaning and listed in order of preference pursuant to August 2015 draft guidance on nonproprietary naming |
| 7/29/2016 | Amgen submits proposed nonproprietary name suffixes |
| 8/10/2016 | Teleconference on nonproprietary name suffixes; FDA cites concerns with proposed suffixes and requests Amgen submit additional nonmeaningful suffixes for consideration |
| 8/12/2016 | Amgen submits three proposed nonproprietary name suffixes and lists "-atto" as preferred suffix |
| 8/19/2016 | FDA deems proposed proprietary name *Amjevita* conditionally acceptable |
| 9/7/2016 | FDA rejects Amgen's preferred suffix "-atto" and two others because they include common medical abbreviations and may present a risk of errors |
| 9/8/2016 | Teleconference on proposed suffixes |
| 9/13/2016 | Amgen submits reconsideration request with additional analyses for proposed suffix "-atto" |
| 9/15/2016 | FDA deems nonproprietary name adalimumab-atto conditionally acceptable |
| 9/23/2016 | FDA licenses Amjevita for all indications on the label of AbbVie's *Humira* (adalimumab) except those protected by orphan exclusivity |
| 9/25/2016 | User fee goal date |

# Sandoz Tested Erelzi's Suffix On Multiple Fronts

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**Sandoz Inc.**'s defense of its preferred nonproprietary name suffixes for the biosimilar *Erelzi* (etanercept-szzs) included a list of analyses conducted to ensure the distinguishable modifiers did not run afoul of FDA guidelines.

As was the case with **Amgen Inc.**'s biosimilar *Amjevita* (adalimumab-atto), Sandoz ran into objections from FDA over its proposed suffixes for Erelzi, which references Amgen's TNF-inhibitor *Enbrel* (etanercept), due to potential confusion with medical abbreviations encompassed within the four-letter suffixes. *(Also see "How To Name A Biosimilar: Amgen Persisted With Amjevita Suffix Despite FDA Doubts" - Pink Sheet, 20 Feb, 2017.)*

Sandoz submitted the Erelzi biologics license application (BLA) on July 30, 2015, approximately one month before FDA released its draft guidance on nonproprietary naming. The guidance described FDA's plans to require that the nonproprietary names for all biosimilars and novel biological products contain a distinguishable, four-letter suffix that was devoid of meaning. *(Also see "FDA Biosimilar Naming Policy Takes Middle-Of-The-Road Approach" - Pink Sheet, 27 Aug, 2015.)*

At the time the 351(k) application was submitted, Sandoz was license holder for the only biosimilar approved in the US. *Zarxio* (filgrastim-sndz), a biosimilar to Amgen's *Neupogen* (filgrastim), was licensed in March 2015 with a distinguishable but meaningful suffix that was derived from the company's name.

Sandoz's BLA for Erelzi "does not include a distinguishing identifier in the proper name," Office of Medication Error Prevention and Risk Management Deputy Director Kellie Taylor said in July 18, 2016 general advice letter to Sandoz. The letter followed FDA's extension of the user fee goal date by three months to Aug. 30.

Taylor requested Sandoz submit for FDA review three different four-letter suffixes that were devoid of meaning pursuant to the recommendations in the August 2015


FDA deemed Sandoz's suffix acceptable less than a week before approving the biosimilar.

company "did not conduct early research on Erelzi to help select a suffix for a biosimilar since the FDA's position wasn't clear" prior to finalization of the naming guidance in January 2017.

## INTERNAL AND EXTERNAL VETTING

Following a teleconference with FDA, Sandoz notified the agency via email on Aug. 5, 2016 of four proposed suffixes, with "-szzs" listed as third in the order of preference.

The company also described the process that it undertook to vet suffixes, noting that a large number of potential suffixes were generated by internal discussion and in consultation with a creative branding agency and a brand name agency.

"Sandoz conducted a series of analyses on the potential suffixes to evaluate whether they had meaning as individual words or could be confused with established abbreviations that are associated with meaning," the company's email to FDA states. "For all potential suffixes, analyses were conducted on both the full four-letter constructs as well as on the first three letters of each potential suffix."

Sandoz listed a series of evaluations made by its staff and an external brand name agency. *(See box, p. 12)*

## '-SZZS' ACCEPTED AFTER FIRST OPTION REJECTED

On Aug. 11, Sandoz informed FDA that "after conducting additional studies" it wanted to move the "-szzs" suffix up in its order of preference, making it number two on the list of four proposals.

On Aug. 25, FDA informed Sandoz that its first suffix choice had been rejected due to inclusion of letters that represent common medical abbreviations, among other reasons. The rejected suffix is redacted from review documents.

However, FDA determined that Sandoz's second choice, "-szzs," was acceptable.

The "-szzs" suffix "is unlikely to be a source of error," Division of Medication Error Prevention and Analysis reviewer Carlos Mena-Grillasca said in an Aug. 24 review.

"The suffix does not suggest any drug substance name or core name designated by USAN council, is not too similar to any other products' suffix designation, does not look similar to the names of other currently marketed products, and does not include any abbreviations commonly used in clinical practice in a manner that may lead the suffix to be misinterpreted as another element on the prescription or order," the review states.

"In addition, the suffix is devoid of meaning and does not make promotional representations with respect to safety or efficacy of this product."

FDA approved Erelzi less than a week later, on Aug. 30. *(Also see "FDA Biosimilar Policy Continues To Evolve With Approval Of Sandoz Erelzi" - Pink Sheet, 30 Aug, 2016.)*

## SUFFIX CHANGES ON THE HORIZON?

Nevertheless, Erelzi's "-szzs" suffix does not appear to pass muster under FDA's final naming guidance released in January. That document added a provision that at least three of the letters in a four-letter suffix must be distinct, a condition which "-szzs" fails to meet. *(Also see "Biologic Product Naming: US FDA Sticks With Suffixes 'Devoid*

*Of Meaning'" - Pink Sheet, 12 Jan, 2017.)*

In review documents for both Erelzi and Amjevita, FDA was careful to note that its determinations on nonproprietary names and suffixes do not constitute or reflect a decision on a general naming policy for biological products, including biosimilars.

Since FDA was still working to finalize a naming guidance at the time Erelzi was under review, "the nonproprietary name is subject to change to the extent that it is inconsistent with any general naming policy for biological products established by FDA," Mena-Grillasca's memo states. "Were the name to change, FDA intends to work with Sandoz to minimize the impact this would have to its manufacture and distribution of this product, should it be licensed."

Zarxio also appears headed for a suffix change. In August 2015, FDA issued a proposed rule to change the suffix to one that is devoid of meaning. However, that rule has not yet been finalized.

Notably, Sandoz and parent company **Novartis AG** have been quite vocal in their opposition to FDA's requirement for distinguishable, four-letter suffixes for biosimilars and other biological products.

"As the pioneer and leader in biosimilars, Sandoz maintains its position that there is no need to assign nonmeaningful, unique suffixes to the nonproprietary names of all currently licensed biologics and those to be licensed in the future," the company said.

"While the FDA contends in its guidance that unique suffixes are necessary to ensure patient safety, we believe that they will not provide additional value beyond that of the current naming system, which has been used successfully for over six decades, and that nonmeaningful suffixes may actually cause confusion among providers that could lead to risks for patients."

The company also maintains that FDA has significantly underestimated the cost burdens for implementing the naming convention. *(Also see "FDA's Burden Estimate On Biologic Naming Ignores Downstream Costs, Critics Say" - Pink Sheet, 16 Feb, 2017.)*

"Our position remains that if the FDA requires suffixes despite the significant financial and resource burden to the applicant and healthcare system, they should be meaningful to avoid confusion and/or risks for patients," the company said.

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### SANDOZ'S CHECKLIST FOR EVALUATING SUFFIXES

- Internet check using google.com and bing.com
- Abbreviation check by use of abbreviations.com and a check of proprietary name databases
- Safety check conducted by drug safety experts
- Trademark check conducted by legal professionals
- Phonetic check conducted by an external brand name agency

NEW PRODUCTS

# FDA's NDA And BLA Approvals: Ganciclovir

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 Biologics** | | | | |
| Exela Pharma SCS | Ganciclovir | 2 mg/mL injection formulation of the antiviral for treatment of cytomegalovirus retinitis in immunocompromised adult patients, including patients with AIDS, and for the prevention of CMV disease in adult transplant recipients at risk for CMV disease. | S, 5 | 2/17/2017 |

| 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 |

# How US Tax Plan Could Affect Global Pharma Manufacturing Networks

**BOWMAN COX** bowman.cox@informa.com

The growing prospects for border-adjusted US tax cuts under discussion in the House of Representatives drew muted responses from pharmaceutical executives in recent earnings calls. Much will depend, after all, on the specifics of a tax plan that could materialize – and on the situation with each company's global manufacturing network.

Meanwhile, there was no discussion at all of the talk of high tariffs that President Trump has brandished at China, Mexico and other US trading partners, and which a landmark analysis by the World Health Organization says would be counterproductive.

## WHO WILL PAY FOR THE BORDER TAX?

The House tax plan reduces corporate income tax to 20% and adds border adjustments exempting exports while taxing imports. Proponents say it will put an end to the recent wave of corporate tax inversions.

As a June 2016 outline of the House tax plan explains, "border adjustments mean that it does not matter where a company is incorporated; sales to US customers are taxed and sales to foreign customers are exempt, regardless of whether the taxpayer is foreign or domestic."

Proponents say the US dollar's value would rise to counter any trade imbalances from the border adjustment. The Tax Foundation, an independent tax policy research organization, on Feb. 15 provided a cogent analysis from this perspective.

But there are opponents, even within the Republican Party. Sen. David Purdue, R-Ga., wrote a letter to colleagues Feb. 8 arguing that the border adjustment is a regressive 20% tax on imports that "hammers consumers and shuts down economic growth."

Purdue, formerly a CEO at Reebok and Dollar General, argued that the expected currency revaluation would in turn reduce the value of foreign investments and hence the savings of American retirees even as their living costs would increase.

As the legislative debate heats up, pharmaceutical manufacturers are beginning to see how the tax plan might affect them.

## 'MINIMAL IMPACT' FOR POST-INVERSION ALLERGAN

**Allergan PLC** was poised to merge with **Pfizer Inc.** in a 2016 tax inversion deal that would have given Pfizer the same tax advantages Allergan obtained in a 2013 merger with **Warner Chilcott PLC** of Ireland. By moving its corporate headquarters from Parsippany, N.J., to Dublin, Allergan reduced its tax rate to 17% from 27%. *(Also see "Tax Benefits, Branded Portfolio, Synergies Drive Actavis' Acquisition of Warner Chilcott" - Pink Sheet, 27 May, 2013.)*

However, the Obama administration's Treasury Department issued rules that rendered such a deal so unattractive that Pfizer last April dropped plans to acquire Allergan. *(Also see "US Treasury Hits Back On Inversions; Will Pfizer Fold?" - Pink Sheet, 4 Apr, 2016.)*

> Sen. David Purdue wrote a letter to colleagues Feb. 8 arguing that a border adjustment is a regressive 20% tax on imports that "hammers consumers and shuts down economic growth."

Asked during a Feb. 8 earnings call if Trump tax cuts would lessen the advantage Allergan had obtained by re-domiciling in Ireland, CEO Brent Saunders gave some reasons why they would not. The Warner Chilcott acquisition was primarily strategic; only secondarily a tax dodge. And in any case, the company has many operations in the US and because it pays tax in the country, it would benefit directly from a US tax rate reduction.

However, border-adjusted corporate taxes proposed in Congress could pose issues, Saunders indicated. "Something that could be detrimental or have a negative effect could be a border adjustment – although minimal," he said.

In any case, Saunders doesn't expect to see tax reform this year.

“But given Roche’s experience with tax reform in Switzerland, CFO Hippe said, “I remain cautious here and I wouldn’t indicate anything at this point which could be of benefit to us.”

## PFIZER REMAINS ANXIOUS FOR US TAX RELIEF

Pfizer CEO Ian Read passed up an opportunity to join other pharmaceutical executives in a Jan. 31 White House meeting with Trump so that he could join a previously scheduled earnings call. On the call, Read emphasized the importance of tax reform to achieving Trump’s oft-stated goal of returning manufacturing to the US.

“We’re driven by the tax code today to manufacture outside of the United States. If there is no penalty by the border adjustment for manufacturing inside the United States to supply your markets outside of the United States, that will encourage us to put more jobs in the United States.”

## BMS: TOO EARLY TO TELL

**Bristol-Myers Squibb Co.** CFO Charles Bancroft admitted the New York-based multinational corporation recently lowered its tax rate by domiciling some of its international intellectual property overseas.

But as to the likely impact of US tax reform, he professed that “it’s way too early for me to comment on how that could play out.”

“There are a lot of different elements that will play into that,” Bancroft said. “Not just IP, but the legal entity structure, supply chain transfer pricing, and where the actual tax rate ends up.”

## ABBVIE DANGLES HUMIRA PROSPECTS

In a Jan. 27 earnings call, **AbbVie Inc.** CFO William Chase said “in the event that there is a tax paradigm that favors US manufacturing,” the company could bring its Humira manufacturing back to the US.

The plant where the company first manufactured Humira is in Massachusetts, he said. The company also has manufacturing facilities in Puerto Rico, which would probably be a better choice.

“We’d have to look closely to whether Puerto Rico is considered part of the U.S., which we obviously think it should be, but if that was the case then it would really be no requirement to move our supply chain around drastically.”

## GSK LAUDS US NETWORK, WAITS ON SPECIFICS

Asked about **GlaxoSmithKline PLC**’s stance on the US border-adjusted tax proposal in light of its recent commitment to build new manufacturing sites in Scotland rather than the US, CEO Andrew Witty called investors’ attention to GSK’s network of nine US manufacturing facilities.

“Whenever we launch a new product … even if it’s initially launched in a factory outside of America, we as quickly as possible transfer production to our US factories,” Witty said during a Feb. 8 earnings call.

Chief Financial Officer Simon Dingemans said much depends on specifics of the border adjustment such as what products it covers and how it covers cross-border flows, “because we’re not alone in having our supply chains stretch across those borders.”

Dingemans said it appears the border adjusted tax “is likely to be a net positive. Exactly how much, impossible to say at this point. But we feel reasonably well hedged, given the manufacturing footprint that Andrew just described.”

He added that Glaxo has the “structural flexibility” to move its various groups, including its research and development investments and intellectual property “to respond to where governments place the incentives.”

## SILVER LINING FOR SANOFI

**Sanofi** would come out better than its peers under the tax scheme, CEO Olivier Brandicourt says.

The French multinational generated 37% of its sales in the US in 2016, while only 26% of that year’s group sales would have fallen under the border tax adjustment, had it been in effect.

Brandicourt also said during a Feb. 8 earnings call that the border-adjusted taxes would have to comply with World Trade Organization agreements. And other regions such as the European Union might respond with measure of their own.

Additionally, Brandicourt suggested human medicines might be exempt from border taxes, as they are from many customs duties.

## ROCHE LESSONS FROM SWISS TAX REFORMS

**Roche** CFO Alan Hippe cautioned during a Feb. 1 earnings call that tax cuts don’t always reduce taxes.

The Basel-based multinational is facing tax reforms in Switzerland intended to establish a more transparent, standardized system by, among other things, removing industry-specific incentives. The net result: Roche’s Swiss taxes will stay the same or increase a little.

About 40% of Roche’s sales and 40% of its operating costs are in the US, Hippe said. “We have invested billions there, we have significant manufacturing in the US … and we’re also a pretty significant taxpayer, yes.”

But given Roche’s experience with tax reform in Switzerland, Hippe said, “I remain cautious here and I wouldn’t indicate anything at this point which could be of benefit to us.”

That said, the company’s global small-molecule manufacturing network is shrinking, while its biologics manufacturing capacity is in a growth spurt, with $800m invested in 2016. The core of that network, obtained in the 2009 acquisition of South San Francisco-based **Genentech Inc.**, is in the US, though not because of any tax incentives.

*From the editors of the Gold Sheet. Published online February 21, 2017*

# Judge Gorsuch Could Be Pharma Ally In FDA Disputes

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Judge Neil Gorsuch's appointment to the Supreme Court would be beneficial to the biopharmaceutical sector given his opposition to giving deference to administrative agencies when laws are ambiguous and his criticism of securities class actions.

Trump nominated Gorsuch to fill the high court's vacancy on Jan. 31. The Senate Judiciary Committee is to begin a hearing on his nomination March 20. Gorsuch was confirmed to the U.S. Court of Appeals for the Tenth Circuit Tenth Circuit by the US Senate in 2006 without opposition.

Attorneys have pored over Gorsuch's opinions and writings to assess how he would rule on cases that come before the Supreme Court. In one decision that could be significant for the pharmaceutical industry, he opposed the "Chevron deference" doctrine, under which courts first determine if a statute is ambiguous and if they find that it is, defer to an agency's interpretation of it. The doctrine is named for the Supreme Court's 1984 decision in Chevron U.S.A. Inc. v. Natural Resources Defense Council Inc.

Attorney James Beck, counsel at Reed Smith, said Gorsuch's views on the doctrine could potentially have an impact on the "intended use" final rule FDA issued in the last days of the Obama Administration. Under the rule, which is included in a final rule on tobacco-derived products, FDA will look at the "totality of evidence" of a manufacturer's intended use of a product. Industry groups asked the agency to stay and reconsider the rule, saying it creates a new legal standard that would allow any evidence to be used to bring a criminal misbranding action against a company. *(Also see "'Intended Use' Rule: Industry Urges US FDA To Revoke 'Totality Of Evidence' Standard" - Pink Sheet, 12 Feb, 2017.)*

"Judge Gorsuch is highly unlikely to let FDA get away with [this] based on his views on administrative deference," Beck stated.

Gorsuch questioned Chevron deference in a 2016 concurring opinion in Gutierez-Brizuela v. Lynch, an immigration case

"There's an elephant in the room with us today," he wrote. "We have studiously attempted to work our way around it and even left it unremarked. But the fact is Chevron and [the 2005 Supreme Court decision] Brand X permit executive bureaucracies to swallow huge amounts of core judicial and legislative power and concentrate federal power in a way that seems more than a little difficult to square with the Constitution of the framers' design. Maybe the time has come to face the behemoth."

> In one decision that could be significant for the pharmaceutical industry, he opposed the "Chevron deference" doctrine, under which courts first determine if a statute is ambiguous and if they find that it is, defer to an agency's interpretation of it.

Judicial deference to FDA is at issue whenever someone challenges an agency decision, such as its decision to pursue an enforcement action or award or deny a product marketing exclusivity. The agency does not always prevail. For example, the court ruled FDA failed to satisfy the Chevron test in rejecting the agency's rationale for denying **Amarin Pharmaceuticals Inc.**'s fish oil pill *Vascepa* (icosapent) five years of marketing exclusivity as a new chemical entity. *(Also see "Legal Briefs: Courts On Exclusivity; Namenda 'Hard Switch' Deemed Coercive; Acorda Fights Bass Patent Petition" - Pink Sheet, 1 Jun, 2015.)*

## 'VAST SOCIAL COSTS' OF SECURITIES FRAUD CLASS ACTIONS

On another issue of importance to drug makers, Gorsuch has been vocal in criticizing securities fraud class actions. While a partner at Kellogg, Huber, Hansen, Todd, Evans & Figel, Gorsuch wrote an amicus brief for the US Chamber of Commerce in the securities fraud case Dura Pharmaceuticals v. Broudo, which the Supreme Court decided in 2005.

In a 2005 paper on settlements in securities fraud class actions published by the Washington Legal Foundation, Gorsuch and co-author Paul Matey described the pressure corporations face to settle meritless suits and the incentives to bring them. The paper was among Gorsuch's extra-judicial writings and speeches compiled by Scotus Blog.

While securities class actions have offered some social benefits, "experience has shown that, like many other well-intended social experiments, they are not exempt from the law of unintended consequences, having brought with them vast social costs never imagined by their early promoters," Gorsuch and Matey wrote.

The life sciences sector is routinely hit with these actions. The law firm Dechert just issued an analysis of the litigation against US-based life sciences companies in 2016. It found that plaintiffs filed 67 class action securities lawsuits against life sciences companies last year, a more than 70% increase from the 39 filed in 2014. About half of them were against companies with a market capitalization of $500m or less. The firm found that nearly 50% of the cases complained of misrepresentations or omissions regarding product efficacy, product safety and/or the likelihood of FDA approval. And several cases alleged misrepresentations about regulatory hurdles and the timing and prospects of FDA approval.

The Supreme Court has issued several rulings on securities fraud cases involving the pharmaceutical industry. In 2010,

in **Merck & Co. Inc.** v. Reynolds, the court clarified when the statute of limitations for filing a suit begins to run and specified that intent to deceive is crucial in determining if a violation occurred. *(Also see "Supreme Court Lets Vioxx Securities Suit Against Merck Stand" - Pink Sheet, 27 Apr, 2010.)*

In 2011, the court ruled in **Matrixx Initiatives Inc.** v. Siracusano that companies can be sued for failing to disclose adverse event reports about their products even if the reports are not statistically significant. *(Also see "Adverse Events Disclosures May Increase After Supreme Court Ruling Against Matrixx, But "Total Mix" Matters" - Pink Sheet, 22 Mar, 2011.)* And in 2013, the court held in **Amgen Inc.** v. Connecticut Retirement Plans and Trust Funds that plaintiffs do not need to prove that a company's misrepresentations were material at the class certification stage. *(Also see "Securities Fraud Class Action Suits Could Grow After Amgen's Supreme Court Loss" - Pink Sheet, 27 Feb, 2013.)*

### POSSIBLE IMPACT ON PRODUCT LIABILITY

Lawyers have also commented on Gorsuch's views on issues pertaining to product liability cases, which often involve the question of whether state tort claims are preempted by federal law. There are two types of preemption, express preemption, in which the law expressly states that a federal law is intended to preempt state legislation, and implied preemption, in which state law conflicts with federal law, or the federal government intended its laws to completely occupy the field it regulates. Express preemption applies to medical devices while implied preemption pertains to pharmaceutical cases.

Gorsuch addressed the issue of express preemption in his 2015 decision Caplinger v. Medronic Inc., which held that a state tort suit alleging defective design and failure to warn regarding the off-label use of a medical device was preempted. Beck said that what this portends for pharmaceutical cases "is up in the air."

Perkins Coie partner Eric Wolff noted in an online post that as a textualist – someone who considers only the words of the law and not the legislators' intent – and defender of the separation of powers, Gorsuch may believe that it is Congress's job to say expressly whether there should be preemption. He said Gorsuch is likely to have a significant effect on the development of law in the admissibility of expert testimony, personal jurisdiction and federal preemption.

Regarding expert testimony, Wolff said Gorsuch appears interested in the gatekeeping role of district courts and has said that courts should not admit speculation just because it comes from a credentialed person. "Gorsuch's views regarding the admissibility of expert testimony may affect product liability litigation because expert testimony is commonplace," Wolff stated.

Prior to his appointment to the Tenth Circuit, Gorsuch had a year stint as principal deputy associate attorney general in the Department of Justice. From 1995 to 2005 he was an associate and partner at Kellogg, Huber. He clerked for Supreme Court Justice Byron White and Justice Anthony Kennedy.

OpenSecrets.org, the website of the Center for Responsive Politics, reports that according to his 2015 financial disclosure statement, Gorsuch has an estimated net worth between $3.2m and $7.3m, not counting things like his Denver-area home. It notes that he earned $217,600 as an appeals court judge and will make $251,800 as an associate justice.

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# Generic Industry Hit With Avalanche Of Price Fixing Suits

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The pressure on generic drug manufacturers is intensifying as investigations by the Department of Justice and state attorneys general have resulted in criminal charges against two former executives and the first government complaint alleging six firms conspired to raise prices and allocate markets.

While drug companies have faced antitrust claims in the past over so-called pay-for-delay deals and product hopping, this is a new and potentially more threatening inquiry as it involves conduct that is inherently unlawful. Companies could be hit with criminal and civil fines and see their executives imprisoned. They are also being deluged with an onslaught of suits by plaintiffs' firms, filed on behalf of indirect and direct purchasers. As of Feb. 10, more than 90 complaints were filed involving 14 generic drugs.

The Connecticut attorney general's office initiated the probe of the generic drug industry in July 2014 when it issued the first subpoenas to generic firms requesting information on their product pricing. Four

months later, the Department of Justice's antitrust division began a parallel criminal investigation issuing subpoenas to firms for information on their pricing and communications with competitors.

The inquiries were overshadowed last year as attention focused on the dramatic price increases of off-patent drugs by **Turing Pharmaceuticals AG** and **Valeant Pharmaceuticals International Inc.** and the presidential election campaign, in which Hillary Clinton, Bernie Sanders, and Donald Trump criticized the brand-name industry for its pricing practices. (*See online timeline of Rx drug pricing probe.*)

But in December the generic industry was once again in the spotlight as the government took the first enforcement actions resulting from the investigations. On Dec. 14, the DOJ unsealed criminal charges against two former **Heritage Pharmaceuticals Inc.** execs for fixing prices, allocating customers and rigging bids. The government said that from about April 2013 until at least December 2015 they and their co-conspirators directed subordinate employees to meet and communicate to discuss the sale of doxycycline and glyburide. *(Also see "Generic Price Fixing Probe: First Charges Unsealed, More May Come Before Inauguration Day" - Pink Sheet, 14 Dec, 2016.)*

The following day, 20 state attorneys general filed suit against Heritage and five other companies – **Aurobindo Pharma USA Inc.**, Citron Pharma LLC, **Mayne Pharma USA**, **Mylan Pharmaceuticals Inc.** and **Teva Pharmaceuticals USA Inc.** – claiming they entered contracts and conspiracies to maintain prices and reduce competition for *Doxy DR* (doxycycline delayed release) and glyburide. More actions against other firms are expected.

Connecticut Attorney General George Jepsen said his office has developed compelling evidence of collusion and anticompetitive conduct across many generic drug companies.

"While our initial lawsuit is pending in federal court, our investigation into this conduct is ongoing, and we are currently partnered with more than 35 states on this investigation," Jepsen said. "We believe the conduct is widespread, involving a significant number of drugs, and we intend to aggressively pursue enforcement of our state and federal antitrust laws to restore competition and integrity to this market."

## CONSPIRACY ALLEGED VIA TRADE SHOWS, DINNERS

The government and Congress began scrutinizing the generic industry following a spike in generic drug prices in 2013.

Sen. Sanders and Rep. Elijah Cummings drew attention to the increases in October 2014 when they sent letters to 14 generic drug manufacturers requesting information about their price hikes. For example, in letters to **Actavis** (now Teva) and Mylan they noted that the firms had increased the price for a 500-count bottle of 100 mg tablets of doxycycline by more than 8,000%, from $20 to more than $1,800. *(Also see "Mylan Joins Firms Facing DOJ Probe On Price Hikes; Senate Plans Industry-Free Hearing" - Pink Sheet, 7 Dec, 2015.)*

The state attorneys general complaint goes into detail in alleging how companies conspired to fix prices and thwart competition for Doxy DR and glyburide. It alleges that Heritage was the "principal architect and ringleader" of a series of conspiracies.

In one instance, the complaint says that when Heritage entered the market for Doxy DR on July 2, 2013, the only other generic manufacturer was Mylan. The complaint alleges that Heritage and Mylan executives agreed to allocate market share and refrain from competing with one another for customers. It says Mylan agreed to "walk away" from at least one large national wholesaler and one large pharmacy chain to allow Heritage to obtain the business and increase its market share.

The complaint asserts that all the defendants sought to avoid communicating with each other in writing, or to delete written electronic communication. It cites emails and text messages, including a June 2014 text message exchange between individuals at Citron and Heritage in which they agreed to raise the price of glyburide. Details about communications, including the names of individuals, are redacted from the complaint.

The complaint claims that the defendants and others in industry have used industry trade shows, including those of the Generic Pharmaceutical Association, to discuss upcoming bids, specific generic drug markets, pricing strategies and pricing terms in their contracts with customers. They also cite interaction at industry dinners and "Girls Night Out" meetings and dinners.

On Feb. 9, the DOJ filed an unopposed motion to intervene in the case, saying it was necessary to protect the integrity of its related ongoing criminal investigation. The department indicated

**VIEW**

**Visit: http://bit.ly/2kULEnR**
for an interactive timeline detailing Rx drug pricing scrutiny by policymakers including Hillary Clinton, Bernie Sanders, and Donald Trump.


Connecticut Attorney General George Jepsen said his office has developed compelling evidence of collusion and anticompetitive conduct across many generic drug companies.

## Generic Drug Price-Fixing Suits

After the Connecticut Attorney General's Office and Department of Justice began investigating the generic drug industry, plaintiffs' firms began filing complaints on behalf of third party payers. As of Feb. 10, there were more than 90 cases alleging price fixing of 14 generic drugs. Below are some of these cases.

| COMPLAINT | ALLEGATIONS |
|---|---|
| In Re: Generic Digoxin and Doxycycline Antitrust Litigation<br>*Eastern District of Pennsylvania, 16-md-02724* | First case filed on March 2, 2016 alleging conspiracy to fix the prices of digoxin and doxycycline. In August, the Judicial Panel on Multidistrict Litigation consolidated 19 cases and transferred them to Eastern District of Pennsylvania for pre-trial proceedings. Allergan, Impax, Lannett Co., Mylan, Par, Sun Pharmaceutical Industries Ltd., and West-Ward Pharmaceuticals Corp. are defendants. Court granted Department of Justice motion to intervene on Jan. 6. |
| In Re: Pravastatin Antitrust Litigation<br>*Eastern District of Pennsylvania, 16-cv-05056* | First two cases filed in September and November were consolidated before Judge Thomas O'Neill Jr. Numerous other cases have been filed by direct and indirect purchasers. |
| Sergeants Benevolent Association Health & Welfare Fund v. Fougera Pharmaceuticals Inc., et al.<br>*Southern District of New York, 16-cv-07229* | Filed Sept. 15, it is the first of 10 cases brought by direct and indirect purchasers against manufacturers of clobetasol pending before Judge William Pauley III. There are also seven cases involving generic desonide and five cases involving fluocinonide pending before him. |
| UFCW Local 1500 Welfare Fund v. Dr. Reddy's Laboratories Inc., et al.<br>*Eastern District of Pennsylvania, 16-cv-06058* | Nov. 17 complaint against five generic manufacturers of anticonvulsant divalproex ER alleges price fixing by Dr. Reddy's, Impax Laboratories, Mylan, Par Pharmaceutical, and Zydus Pharmaceuticals (USA) Inc. |
| UFCW Local 1500 Welfare Fund v. Actavis Holdco US Inc., et al.<br>*Southern District of New York, 16-cv-09431* | Dec. 6 complaint alleges Actavis, Fougera Pharmaceuticals, Perrigo New York Inc., Sandoz Inc., and Taro Pharmaceuticals USA Inc. fixed the price of desonide topical cream and ointment products. |
| USA v. Glazer<br>*Eastern District of Pennsylvania, 16-cr-00506*<br>*USA v. Malek*<br>*Eastern District of Pennsylvania, 16-cr-00508* | On Dec. 14, Department of Justice unsealed charges against two former Heritage executives for conspiracy to fix prices and allocate customers for antibiotic doxycycline and diabetes drug glyburide. |
| State of Connecticut v. Aurobindo Pharma USA Inc., et. al<br>*District of Connecticut, 16-cv-02056* | 20 state attorneys general filed Dec. 15 complaint against Heritage, Aurobindo Pharma USA Inc., Citron Pharma LLC, Mayne Pharma USAA, Mylan Pharmaceuticals Inc. and Teva alleging market allocation and price fixing agreements for glyburide and Doxy DR (doxycycline delayed release). |
| 1199 SEIU National Benefit Fund v. Lannett Co., Mylan Pharmaceuticals<br>*Southern District of New York, 16-cv-09666* | Dec. 14 complaint alleges conspiracy to raise price of generic levothyroxine hormone replacement tablets; additional suits have been filed. |
| FWK Holdings LLC v. Actavis Elizabeth LC, et al<br>*Southern District of New York, 16-cv-09901* | Filed Dec. 23, it is one of several suits alleging price fixing of generic propranolol. Defendants include Teva, Pliva, Mylan, UDL Laboratories, Endo, Par, Heritage, Breckenridge Pharmaceuticals, Upsher-Smith Laboratories |
| NECA-IBEW Welfare Trust Fund v. Actavis HoldCo US Inc., Lannett Co. and Epic Pharma LLC<br>*District of New Jersey, 17-cv-00629* | Jan. 30 complaint alleges defendants engaged in agreement and conspiracy to artificially raise and maintain prices of ursodiol, prescribed for gallbladder stone dissolution. |

that further actions were to follow, saying it had unsealed "the first criminal charges" in the investigation. The defendants, former Heritage CEO Jeffrey Glazer and former president Jason Malek, pled guilty to the charges on Jan. 9 and are to be sentenced on Sept. 28.

## 'ACTING RESPONSIBLY' BY RAISING DRUG PRICES

The generic drug industry is sensitive to the pricing controversy. At its annual meeting in Orlando, GPhA announced a rebranding campaign and renamed itself the Association for Accessible Medicines. *(Also see "GPhA Rebrands As AAM, Hopes To Change Tenor Of Drug Pricing Debate" - Pink Sheet, 14 Feb, 2017.)*

While the association is promoting the generics industry as driving savings rather than costs, the lawsuits convey a different image.

A complaint by an employee health and welfare benefit plan against levothyroxine manufacturers **Lannett Co. Inc.** and Mylan alleges that the companies formed a price-fixing cartel that included all their levothyroxine products. As evidence, the complaint includes charts of Medicaid reimbursement per unit for dosages of generic levothyroxine and comments Lannett CEO Arthur Bedrosian and Mylan CEO Heather Bresch made on earnings calls.

The government actions in December have led to a surge of suits, most of which are on behalf of health and welfare funds. They target generic manufacturers of 14 drugs, including clobetasol, clomipramine, desonide, divalproex, fluocinonide, pravastatin, propranolol, and ursodiol.

The complaint says that in a Sept. 10, 2013 earnings call, Bedrosian was asked for his reaction to Mylan increasing the price of levothyroxine "quite significantly," and he replied, "You mean after I sent them the thank you note?"

According to the complaint, Bedrosian then said, "So whenever people start acting responsibly and raise prices as opposed to the typical spiral down of generic drug prices, I'm grateful." He also said of two possible competitors that he hoped they would be responsible and not go into the marketplace.

The complaint also quotes remarks Bresch made on May 2, 2013 that some prices were "literally cheaper than dirt for some of these older products," and that the bar "needs to go up and get rebalanced from a pricing perspective."

The complaint, 1199 SEIU National Benefit Fund v. Lannett Co., was filed in the Southern District of New York on Dec. 14, the same day the DOJ brought felony charges against the former Heritage execs. The complaint cites the DOJ charges and links its allegations to the broad DOJ probe of the industry.

Plaintiffs firms began suing generic firms after the state AGs and DOJ began their investigations. The first complaint brought on behalf of indirect purchasers was filed on March 2, 2016 against manufacturers of digoxin and doxycycline. Numerous other complaints followed and in August they were consolidated in mulitidistrict litigation. The DOJ has intervened in this litigation as well.

The government actions in December have led to a surge of suits, most of which are on behalf of health and welfare funds. They target generic manufacturers of 14 drugs, including clobetasol, clomipramine, desonide, divalproex, fluocinonide, pravastatin, propranolol, and ursodiol. (*See chart, p. 18.*)

## BRAND-NAME COMPANIES FACE DIFFERENT SCRUTINY

While brand-name companies have been sharply criticized for their drug pricing, they are free to set whatever price they wish for their products and are not subject to price fixing claims. However, a consumer class action lawsuit against three insulin manufactures is trying to make a case against pricing behavior based on other legal grounds.

The complaint alleges that **Sanofi**, **Eli Lilly & Co.** and **Novo Nordisk AS** violated the Racketeer Influenced and Corrupt Organizations Act and state consumer protection laws by unlawfully engaging in a scheme to inflate the benchmark prices of rapid- and long-acting analog insulin drugs and then marketing the spread between the benchmark prices and real prices to pharmacy benefit managers, causing consumers to overpay for them. *(Also see "Diabetes Rebate Model Challenged On Morality Grounds In Class Action Suit" - Pink Sheet, 31 Jan, 2017.)*

There appears to have been some conflict between plaintiffs' firms over the litigation. The suit was filed in the District of Massachusetts by Hagens Berman Sobol Shaprio on Dec. 30 and then dismissed on Feb. 2. In a notice to the court, Hagens said that another action over the same conduct had been filed first in the District of New Jersey. On Feb. 2, the same plaintiffs filed a similar suit against the same companies in the US District Court for the District of New Jersey. They are now represented by Carella, Byrne, Cecchi, Olstein, Brody & Agnello.

Like the initial suit, the new complaint states that insulin drugs that used to cost $25 per prescription now cost between $300 and $450 and some patients now pay almost $900 per month.

For decades, brand-name firms have faced government investigations for their marketing behavior, with the focus on off-label promotion and kickback allegations. The subject of the probes has shifted in recent years and companies are now facing investigations about their patient assistance programs, support of non-profit organizations, and contractual agreements with pharmacy benefit managers. *(Also see "Pharma Pricing, Non-Profit Ties Get Increasing Scrutiny From Prosecutors" - Pink Sheet, 14 Sep, 2016.)*

But the heat is now on the generic drug industry. The extent of the fallout remains to be seen with the future actions of the state AGs and DOJ. If history is any indication, it will be costly and bruising.

*Published online February 22, 2017*

# FDA's ANDA Approvals

| SPONSOR | ACTIVE INGREDIENT | DOSAGE; FORMULATION | APPROVAL DATE |
|---|---|---|---|
| Atlas | Methocarbamol | 500 mg and 750 mg; tablet | 2/8/2017 |
| Accord | Carboplatin | 500 mg/5 mL (10 mg/mL), 150 mg/15 mL (10 mg/mL), 450 mg/45 mL (10 mg/mL), and 600 mg/60 mL (10 mg/mL); injectable, IV infusion | 2/9/2017 |
| Mylan | Estradiol/ norethindrone acetate | 0.5 mg/0.1 mg and 1 mg/0.5 mg; tablet | 2/10/2017 |
| Gland | Oxaliplatin | 50 mg/10 mL (5 mg/mL) and 100 mg/20 mL (5 mg/mL); injectable, IV infusion | 2/10/2017 |
| Cipla | Oxaliplatin | 50 mg/10 mL (5 mg/mL) and 100 mg/20 mL (5 mg/mL); injectable, IV infusion | 2/10/2017 |
| Novel | Homatropine methylbromide/ hydrocodone bitartrate | 1.5 mg/5 ml and 5 mg/5 mL; syrup | 2/13/2017 |
| Cadila | Rivastigmine tartrate | EQ 1.5 mg base, EQ 3 mg base, EQ 4.5 mg base and EQ 6 mg base; capsule | 2/13/2017 |
| Actavis | Levoleucovorin calcium | EQ 50 mg base/vial; powder, IV infusion | 2/13/2017 |
| Amneal | Levoleucovorin calcium | EQ 50 mg base/vial; powder, IV infusion | 2/13/2017 |
| Gland | Tranexamic acid | 100 mg/mL; injection | 2/13/2017 |
| Novel | Moxifloxacin HCl | EQ 400 mg base; tablet | 2/13/2017 |
| Teva | *Logilia* (ulipristal acetate) | 30 mg; tablet | 2/13/2017 |
| Mylan | Zoldedronic acid | EQ 5 mg base/100 mL; injectable, IV infusion | 2/14/2017 |
| **Tentative Approvals** | | | |
| Mylan | Bivalirudin | 250 mg/vial; injectable | 2/10/2017 |
| Sun | Tadalafil | 2.5 mg, 5 mg, 10 mg and 20 mg; tablet | 2/10/2017 |

# How EMA's Adaptive Pathways Fits Into The Complex Drug Pricing Puzzle

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There are suggestions that EU regulatory initiatives aimed at bringing innovative medicines to the market faster, especially where the medicines address areas of high unmet medical needs and rare diseases, may also play a role in lowering the prices of orphan drugs. There is, however, no evidence that this has happened as yet. Health technology assessment bodies and payors point out that such initiatives are only one part of the complex drug reimbursement puzzle, and that it might be difficult to assess the direct impact of such early access initiatives on drug pricing.

The European Medicines Agency's adaptive pathways project – which can result in eligible drugs being authorized earlier on in the development process for a limited population – is an example of an initiative that some say could help bring down drug orphan drug prices. "It should. I am not saying it does, but in our view we think that it should," said Yann Le Cam, chief executive officer of EURORDIS, the patient-driven alliance of rare disease organizations in Europe.

Le Cam's reasoning is based on the fact that under such accelerated review initiatives, companies can get their products to market earlier, potentially with conditional approval. "This is usually at the end of Phase II [trials]… because after that you want to generate real world evidence and have more knowledge about the efficacy and effectiveness of the product," Le Cam told reporters during a virtual press conference on Feb. 22 that was organized on the sidelines of EURORDIS's multi-stakeholder symposium on Improving Patients' Access to Rare Disease Therapies.

This, in turn, means that the investment that is needed to support the approval process is lower for such products compared to drugs authorized under conventional conditions. That should help lower development costs and therefore the market price, says Le Cam, but a practical demonstration of this concept actually leading to cheaper medicines "as far as I know has not been done," he added.

Payors point to the complexity of the issue. Ri de Ridder, the director general of Belgium's National Institute for Health and Disability Insurance (RIZIV-INAMI), does not believe that "just one change in the decision chain will automatically lead to another outcome – that is lowering of drug prices".

De Ridder, who also addressed the press conference, said that several questions needed to be addressed at the point of reimbursement decision, such as how to manage the many uncertainties that exist, how to be best informed about the value of the medicine based on available knowledge and how to translate that into something which would be an acceptable cost for society.

Over the past 10 years, said de Ridder, there has been a huge change in how reimbursement decisions are dealt with for new medicines, including orphan drugs. In Belgium, for example, he explained that the entry of new innovative medicines is now handled through managed entry agreements. Decisions are no longer based "on the classical pathway of having an HTA and an economic evaluation… It is much more fluid now", he said.

**The adaptive pathways initiative is being followed by "adaptive reimbursement negotiated contracts" and this approach will likely undergo more changes in the future, Belgium's de Ridder said.**

The adaptive pathways initiative is being followed by "adaptive reimbursement negotiated contracts" and this approach will likely undergo more changes in the future, de Ridder said. As such, he believes that the EMA's adaptive pathways initiative alone cannot lead to lowered prices. To achieve price reductions, he explained, there is a need to redesign the entire process so that it leads to "fair decisions [on] meeting patients' expectations… and also give[s] the guarantee that what we are investing in terms of money is the best investment we can make for everyone".

Sheela Upadhyaya from UK HTA body NICE, believes that it is very hard to demonstrate the improvements that initiatives such as the adaptive pathways project can deliver in terms of price reduction. Upadhyaya emphasized the need for a "more holistic, wider concept" that would need buy-in and engagement from the industry, payors, HTA bodies and patient groups.

"It's not just one process that is going to allow us to make those changes and reduce the prices… The adaptive pathways element is one small piece of the puzzle and we need to think how we can enhance and build on that in order to enable [patient] access to be a more real scenario," said Upadhyaya, who is associate director for highly specialized technologies at NICE's Centre for Health Technology Evaluation.

*From the editors of Scrip Regulatory Affairs. Published online February 23, 2017*

# Belgium To Test Parallel Review Of Clinical Trial Dossiers Ahead Of New Regulation

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Belgium's Federal Agency for Medicines and Health Products is preparing to launch a pilot later this year under which it plans to review clinical trial applications in parallel with national ethics committees and within the strict timeframes specified in the upcoming EU Clinical Trials Regulation.

The FAMHP explained that while the voluntary pilot would be conducted under Belgium's current national clinical trials legislation of May 7, 2004, the evaluation of clinical trial dossiers included in the pilot "would follow the spirit" of the CTR that is set to come into force in October 2018. *(Also see "Training For 'Huge' EU Clinical Trials Portal And Database On Track For 2017" - Pink Sheet, 6 Jan, 2017.)*

Sponsors interested in participating in the pilot can still send in their proposals to ct.rd@fagg.be even though the official deadline for companies to sign up ended on Jan. 24, an FAMHP spokesperson told the *Pink Sheet* that. The selection of trials to be included in the pilot is to be confirmed by the FAMHP and the "college" of ethics committees that will be established in the future.

The selection of trials for the pilot will depend on the available capacity at both the FAMHP and the ethics committees and on the added value that such testing would bring. There is no restriction on the types of clinical trial applications that can be submitted under the pilot as it includes both national and multi-national trials as well trials evaluated under those voluntary harmonization procedures (VHPs) for which Belgium is the reference member state, the spokesperson clarified.

The response from sponsors to the pilot to date has been quite good with commercial as well as non-commercial sponsors submitting applications, the spokesperson said. The agency is aiming to evaluate a batch of 10 trials representing different types of applications.

The pilot is expected to help the FAMHP identify any potential obstacles involved with assessing applications under the CTR processes and timelines so that it can streamline its procedures before the new regulation enters into force. The first tests under the pilot are expected to begin in October/December 2017.


"The pilot is expected to help the FAMHP identify any potential obstacles involved with assessing applications under the CTR processes and timelines so that it can streamline its procedures before the new regulation enters into force.

Germany and France have undertaken similar preparatory pilots to develop and test procedures in anticipation of the CTR. *(Also see " German Pilot Seeks Companies To Test EU's Future Clinical Trial Application Procedure " - Pink Sheet, 29 Oct, 2015.)(Also see "French To Test Future EU Clinical Trial Procedures For Drugs" - Pink Sheet, 6 Oct, 2015.)*

The Belgian pilot is expected to commence in March this year, when the government amends the existing 2004 clinical trials legislation to change, among other things, the provisions relating to ethics committees. Under the CTR, the review of clinical trial dossiers by the national competent authority and the ethics committee will have to run in parallel so that they are able to issue a consolidated single decision within a short timeline.

To ensure coordination between the FAMHP and the 24 accredited ethics committees currently functioning in Belgium, the government plans to establish a "college" of ethics committees in the near future. The college, which will be hosted by the Federal Public Service (Public Health), will be an independent entity and will act as a contact point between the FAMHP and the ethics committees.

The college will coordinate the working of the ethics committees and will be responsible for their quality assurance. The college will "support the ethics committees and attempt to harmonise their way of working," the FAMHP spokesperson said.

In addition, to support the ethics committees, the government is developing a royal decree for the accreditation of ethics committees to enable them to evaluate clinical trials with medicinal products under the upcoming CTR, the spokesperson added.

*From the editors of Scrip Regulatory Affairs. Published online February 20, 2017*

# Pediatric Drug Development A Priority For US FDA's New Oncology Center Of Excellence

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Accelerating the development of pediatric cancer therapeutics and diagnostics will be a key focus for the US FDA's new Oncology Center of Excellence (OCE).

"As part of the newly formed Oncology Center of Excellence, one of our top priorities is to do what we can to help move pediatric oncology drug development forward," Division of Oncology Products 2 Acting Associate Director Martha Donoghue said Feb. 21 at a Friends of Cancer Research meeting on pediatric drug development.

"We have at last count now about 17 or 18 pediatric hematologists/oncologists on staff" with varying areas of expertise, and "we are all committed to doing our part as regulators and as resources to the pediatric oncology community … to move things forward."

Donoghue's comments suggest an early focus for the OCE, a new center that will leverage the regulatory and review expertise across FDA's medical product centers. OCE is aimed at expediting the development of oncology and malignant hematology-related medical products and supporting an integrated approach in the clinical evaluation of drugs, biologics and devices for cancer.

OCE's creation was announced in June as part of the federal Cancer Moonshot Initiative. At that time, FDA Office of Hematology and Oncology Products (OHOP) Director Richard Pazdur was named as acting director. *(Also see "FDA's Pazdur Jumps Over To New 'Moonshot' Role" - Pink Sheet, 29 Jun, 2016.)*

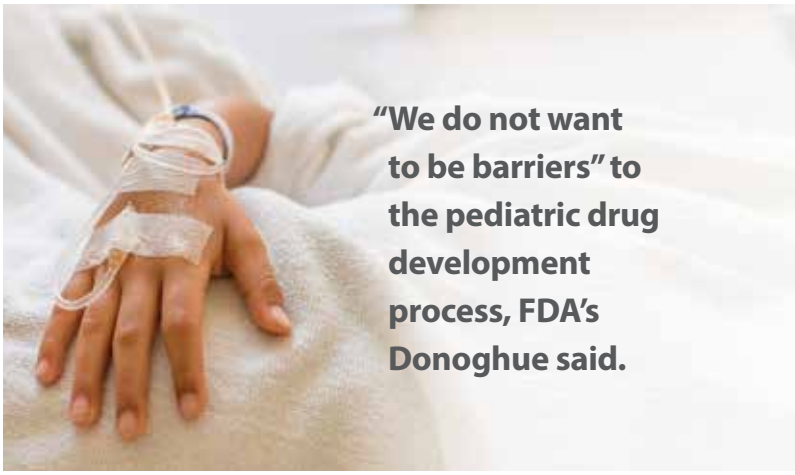
FDA has since removed the "acting" from Pazdur's title. On Jan. 19, then-FDA Commissioner Robert Califf announced OCE's formal launch and Pazdur's appointment as the center's permanent director. The announcement came on Califf's last full day as commissioner and was part of a rush of FDA operational and regulatory news ahead of the Jan. 20 inauguration of President Donald Trump. *(Also see "FDA's Document Dump: Guidance Release Skyrockets Ahead Of Trump's Arrival" - Pink Sheet, 22 Jan, 2017.)*

Pazdur is expected to retain his duties as OHOP director. *(Also see "FDA's Pazdur To Retain Drug Approval Duties In Oncology Center Of Excellence" - Pink Sheet, 7 Nov, 2016.)*

## CENTER ORGANIZATION STILL A WORK IN PROGRESS

Despite the official launch announcement, FDA has publicly shared few details about the new center's operating framework and structure. "FDA is taking important steps to formalize the structure and implementation of the OCE as part of its overarching effort to better address the needs of cancer patients, through reorganization within the FDA's Office of Medical Products and Tobacco," Califf's Jan. 19 announcement states.

It seems that even those on the inside aren't yet exactly sure what the new center will look like. "That structure of the OCE isn't made public yet and, frankly, I don't know a lot of the information myself," Donoghue said. "But I do know that one thing that we're prioritizing is trying to increase the efficiency of working between centers."



**"We do not want to be barriers" to the pediatric drug development process, FDA's Donoghue said.**

For example, she noted that pediatric devices and in vitro diagnostics is "a huge area of unmet medical need" and will be a focus for greater intra-agency collaboration and coordination under OCE. "I do think that what will come out of this new system is more streamlined and more open and unified communication from the agency on these issues, because we recognize that development plans really require … coordination with all of those aspects, and that's something we're giving priority to."

## OPTIMIZING EXISTING REGULATORY AUTHORITY …

The Friends of Cancer Research meeting served as a forum for discussion on use of master trial protocols as a way to overcome challenges inherent in pediatric cancer drug development.

Among FDA speakers at the meeting, a common refrain was the agency's desire to maximize its regulatory authority in a way that serves not as a roadblock but, rather, helps move development of new pediatric cancer therapeutics forward more quickly.

The agency staffers' comments to a generally friendly audience may be viewed as a counterpoint to President Donald Trump's view that FDA is not doing enough to accelerate drug approvals and his announced, but still unspecified, plans to streamline the agency and lift some of industry's regulatory burdens. *(Also see "Trump Promises Changes To 'A Lot Of Rules' At US FDA" - Pink Sheet, 31 Jan, 2017.)*

"We're cognizant of the fact that we do not want to be barriers" to the pediatric drug development process "and we want to do what we can to help promote the process," Donoghue said. "Part of that is leveraging our existing regulations which are primarily incentive programs and we are working on doing that to the best of our ability."

FDA has been "very proactive in promoting a collaborative approach to timely pediatric drug development," said Gregory Reaman, OHOP associate director for oncology sciences.

"We can only do what we are authorized to do by legislation. We have no other mechanism by which to operate," Reaman said. "But we can optimize as best we can that regulatory authority, so we have been proactively attempting to identify new, promising products, engage with industry and academia early, as well as advocacy groups to study these promising products and hopefully harnessing regulatory science."

The agency wants industry sponsors to start conducting pediatric studies earlier in a drug's development. Ideally, pediatric studies should be initiated immediately following adult Phase I studies if a scientific rationale for pediatric use exists, Reaman said. "We're not quite there yet," but we're "getting closer."

Toward this end, FDA has been issuing written requests for studies under the Best Pharmaceuticals for Children Act (BPCA) earlier in the development process. Sponsors who complete studies in response to a BPCA written request are eligible for six months of marketing exclusivity for an approved drug.

In the past, written requests often were not issued until after drug approval. "We're now trying to issue written requests before new drug applications come in," Reaman said.

Written requests also can be used to spur and reward innovative trial designs and development strategies.

"We've actually issued a written request to a sponsor for embedding a pediatric trial in an adult study that will probably only accrue a handful of patients, so I think this is really pretty novel," Reaman said.

## ... WHILE EYEING AN EXPANSION OF PREA

Reaman bemoaned the lack of impact that the Pediatric Research Equity Act (PREA) has had on pediatric cancer drug development. Under PREA, FDA can require studies in pediatric populations specific to the adult indication for which the drug is under review.

"The unfortunate thing is it applies only to indications included in the submission," Reaman said. In addition, "drugs with orphan designation are exempted from PREA. Forty percent of new oncology products in the last three years have received orphan designation."

"Essentially PREA has no relevance to pediatric cancer," Reaman said, although the agency would like to see this dynamic change.

"Expanding the authority of PREA is clearly something that we've talked about," Reaman said. "Requiring studies based on molecular mechanism of action could certainly increase the number of pediatric studies under PREA."

Legislation introduced in the House and Senate in 2016 would do just that; the RACE for Children Act would require pediatric studies based upon a drug's molecular target and eliminate the pediatric study exemption for drugs approved in rare adult cancers. *(Also see "Pediatric Study Requirements For Cancer Have FDA Support, But Pose Industry Challenges" - Pink Sheet, 3 Aug, 2016.)*

Although the companion bills never made it out of their respective committees in the House and Senate, they are expected to be reintroduced soon and could find their way into legislation reauthorizing the prescription and generic drug, biosimilar and device user fee programs that must be enacted before the existing programs expire Sept. 30.

## DRUGS WITHOUT AN ADULT INDICATION

Most pediatric cancer drug development is inextricably tied to use in adults, but there currently is no "legislative fix" for investigational agents whose usefulness is limited to the pediatric setting, Reaman said.

While there are "very meaningful and early incentives to industry," such as the pediatric rare disease priority review voucher program, these "require more evaluation," Reaman said.

FDA is not a fan of the pediatric rare disease and tropical disease priority review voucher programs, saying that they have adversely impacted its ability to set public health priorities and effectively manage its workload. *(Also see "Review Voucher Program For Rare Pediatric Diseases Should Not Be Reauthorized, FDA Says" - Pink Sheet, 2 Mar, 2016.)* Although FDA did not support reauthorization of the pediatric rare disease voucher program, Congress renewed it until 2020 as part of the 21st Century Cures Act and also established a new voucher program for medical countermeasures. *(Also see "The Evolution Of 21st Century Cures Legislation" - Pink Sheet, 29 Nov, 2016.)*

**Sarepta Therapeutics Inc.**'s recent sale of a voucher for $125m suggests the growing number of vouchers awarded by the agency could be depressing their value on the open market. *(Also see "Gilead Buys Its Third Priority Review Voucher, But Is The Mania Over?" - Pink Sheet, 21 Feb, 2017.)*

A better option for incentivizing novel pediatric drug development may be found in optimizing the Orphan Drug Act, "which in my opinion is not adequately taken advantage of in pediatric cancer," Reaman said. The Orphan Drug Act provides a host of financial incentives, seven years of marketing exclusivity and more regulatory flexibility, he noted.

"I think this is something that really could benefit pediatric drug development particularly since nearly 40% of all oncology products are designated orphan drugs, and what could be a bigger orphan than children?"

Donoghue urged sponsors to talk to FDA early about the designing the most efficient drug development program possible, particularly in cases where an adult indication is not being pursued.

"We want to be resources to help small companies [and] big companies that may have a first-in-pediatric drug that may not work for any adult cancer figure out a feasible way to move their drug development forward in a way that that can be accomplished," Donoghue said.

"And that doesn't necessarily mean a clinical trial of 100 patients," she continued. "If we have a drug that we think will work and has a big signal and it's for a rare cancer, it may not and should not require studying 100 patients or more. It really just depends. And I think early communication with us, helping us partner with you in designing the most efficient drug development program possible, is a top priority for us."

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# Is Takeda's Consumer Unit 'Agile' Enough To Stretch Outside Japan?

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**Takeda Pharmaceutical Co. Ltd.**'s created a subsidiary a year ago to make the Japanese firm more "agile" in the OTC drug and vitamin and mineral product markets. Now it is spinning off the consumer product portfolio into the wholly owned and independent subsidiary, with ambitions to boost revenues and expand operations beyond Japan.

The unit will handle a product portfolio larger than many older consumer firms. Still, all signs continue to point to the firm's Rx operations as its predominant revenue drivers. Analysts tracking the firm's performance generally don't spare even a glancing nod to its OTC drug and vitamin/mineral sales as they emphasize that earnings growth relies on its prescription product pipeline and on pharma sales in Japan, which is the second-largest drug market and accounts for 40% of Takeda's current business but where overall sales are expected to be flat over the next 10 years.

Osaka-based Takeda on Feb. 20 announced that on April 1 it is transferring its Japan consumer health care business unit to **Takeda Consumer Healthcare Co. Ltd.**, the subsidiary it launched in February 2016 as the eventual home of its consumer product operations.

Takeda stated that the business it is transferring to Takeda Consumer had revenues of JPY 81.9m ($720,600) and operating profit of JPY 17.9m ($158,000) during the firm's fiscal 2015.

The business markets products in more than 15 categories, from OTC drugs for cold relief and gastrointestinal discomfort to nutrient and tonic drinks and Japanese kampo, or herbal products, according to Takeda's website. It makes brands including *Benza* cold remedies and the *Alinamin* vitamin line and has license from **GlaxoSmithKline PLC** to market *Nicorette* brand nicotine replacement therapy products *(see table. p. 26)*.


*Alinamin EX Plus for physical and visual fatigue and soreness is one of the band's products with wide-raning indications included in Takeda's consumer health portfolio.*

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## FROM JAPAN TO PAN-ASIA?

Despite the size and variety of its portfolio, Takeda's presence in the consumer product space largely is limited to Japan.

With the consumer health market the only focus of Takeda Consumer, the business likely now has a better chance of increasing its product distribution to meaningful levels outside Japan. In its release, Takeda said Takeda Consumer intends to expand product distribution and "become a leading company in the consumer health care markets of the Asian region."

Takeda Consumer also gives Takeda's consumer business a better home for developing even more product types.

Takeda said it has planned to spin-off Japan Consumer Healthcare to Takeda Consumer "to realize a more agile business model to promptly meet environmental changes and customers' needs" in the "constantly changing" consumer health market, with consumers' needs "becoming more and more diversified."

Takeda Consumer President Masashi Sugimoto says the spin-off "will allow the business unit to respond rapidly to consumers' needs by taking advantage of various business opportunities" and "will continue to contribute to Takeda's growth by accelerating the growth of the" subsidiary.

For bookkeeping purposes, Takeda plans to transfer all shares of a second wholly owned subsidiary, **Takeda Healthcare Products Co. Ltd.**, to Takeda Consumer, which is based in Tokyo. The transfer makes Takeda Healthcare Products, established in 1980, a wholly owned subsidiary of Takeda Consumer.

## WHITHER TAKEDA CONSUMER MOVE?

Analysts are not hailing the spin-off as a notable boost for Takeda's prospects. The consumer move is part of the firm's overhaul, but not one expected to generate significant results nor one that merited analysts' mention when Takeda unveiled its plan a year ago or with its latest announcement.

In a Feb. 21 update on her overview of Takeda, Morningstar analyst Karen Andersen said "headwinds could be steep for Takeda, given expanding generic drug penetration targets in Japan, future novel competition, and the firm's weak in-house pipeline."

Andersen said Takeda is expanding from marketing products predominantly in Japan and moving past the US patent expiration of blockbuster diabetes therapy Actos largely through its 2011 acquisition of *Nycomed SPA* and the pending acquisition of *Ariad Phar-*


*The diverse Hicee vitamin/mineral/herbal line, including this product for skin health and physical stamina, is among the products spanning 16 consumer health categories in Takeda's portfolio.*

*maceuticals Inc.* through a deal announced in January. *(Also see "Takeda Acquires Ariad In $5.2bn Deal – US Infrastructure A Key Component?" - Scrip, 9 Jan, 2017.)*

Her research note states Morningstar expects Takeda to average annual top-line growth of 2.5% through 2020 as generic penetration increases in Japan and generics launch in the US in 2018 of *Velcade* (bortezomib).

The analysts expect Takeda's adjusted earnings per share to increase 3.1% on average annually over the period because its cost-saving plan and higher-margin products like *Entyvio* (vedolizumab) and *Ninlaro* (ixazomib) "will only slightly outweigh pressure on margins from the loss of long-listed drugs in Japan" as part of the country's reform to its health care system spending.

Velcade and Ninlaro are indicated for multiple myeloma, both after initial treatments with other drugs and Ninlaro also to be used in combination with lenalidomide and dexamethasone. Entyvio is for moderately to severely active ulcerative colitis. *(Also see "Evolving Takeda Signals Intent To Build Around Entyvio, GI Franchise" - Pink Sheet, 11 Jul, 2016.)*

"While the Japanese government has taken steps to reduce corporate tax rates and improve reimbursement for innovative drugs, debt levels are twice the size of the country's economy, and cost-cutting measures in healthcare could become more extreme due to slow economic growth and an aging demographic," Andersen said.

*From the editors of the Tan Sheet.*
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## From Alinamin to Splie

Takeda Consumer starting April 1 will make and market brands that span diverse consumer health categories, in the nonprescription drug and vitamin/mineral spaces, and will continue marketing some OTC drug brands corporate parent Takeda Pharmaceutical has licensed from other pharmas. Some products known as OTC drugs in the US and some other countries are identified in Japan as quasi-drugs, formulations that have minimal to moderate pharmacologic activity but still are approved for specific indications.

| CATEGORY | BRANDS |
|---|---|
| Vitamins/minerals/nutrients and tonic drinks | Alinamin, Actage, Hicee, Takeda, Shin Calcichew, Panvitan, Tocorl, Fromin Ace, Benza |
| Antitussives/expectorants | Benza, Aneton |
| Sore throat | Benza |
| Rhinitis | Benza, Aneton, Cor-Tyzine |
| Dermatology preparations | Terres, Terra, Terra-Cortl, Terramycin, Lovac, Osvan |
| Laxatives | Takeda Kampo, Herb-in Takeda, Clear |
| Gastrointestinal | That's, Takeda Kampo |
| Antipyretic analgesics | Feria, Grelan, Doxin, Tylenol |
| Motion sickness | Takeda Morimonoyoidome |
| Hemorrhoids | Borraginol, Naifuku Borraginol |
| Ophthalmic | Mytear, Newmytear, Firstmytear, MytearClean, Mytear Fresh, Mytear Vitamin, Visine |
| Japanese kampo formulations | Stlage, Rubina, Rockmin |
| Medicated bath salts/medicated soap | Shanlove |
| Skin- and body-care products | Splie, Terres |
| Nicotine replacement therapy | Nicorette |
| Cold remedies | Benza |

# Recent And Upcoming FDA Advisory Committee Meetings

| TOPIC | ADVISORY COMMITTEE | DATE |
|---|---|---|
| Pediatric-focused safety reviews for various products as mandated by the Best Pharmaceuticals for Children Act and Pediatric Research Equity Act; role of pharmacogenomics in pediatric product development | Pediatric | March 6-7 |
| Strain selection recommendations for influenza virus vaccines for the 2017-2018 flu season | Vaccines and Related Biological Products | March 9 |
| Premarketing and postmarketing data about the abuse of Endo's *Opana ER* (oxymorphone extended-release), and abuse of generic extended-release and immediate-release oxymorphone products | Drug Safety and Risk Management; Anesthetic and Analgesic Drug Products | March 13-14 |
| Strategies, approaches and challenges in model-informed drug development, including use of physiologically-based pharmacokinetic modeling and simulation throughout a drug's life cycle and mechanistic model-informed safety evaluations | Pharmaceutical Science and Clinical Pharmacology | March 15 |

Pink Sheet

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