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# HHS Leadership Upheaval Could Delay Initiatives Impacting Biopharma

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A presidential executive order on drug costs and Medicare payment experiments for prescription drugs are a couple of the pending biopharma-related initiatives that now become the responsibility of HHS Acting Secretary Donald Wright with the departure of Tom Price.

The White House announced Price's resignation Sept. 29 and said he will be succeeded on an acting basis by current HHS Acting Assistant Secretary for Health Don Wright.

Price resigned amid intensifying public criticism over his use of taxpayer funded chartered planes while carrying out his duties. His departure also followed repeated failures to move one of the Administration's top priorities – legislation to repeal and replace the Affordable Care Act – in the Senate.

An experienced HHS official, Wright served as HHS principal deputy assistant secretary for health from 2007-2009, under President George W. Bush. He is also currently deputy assistant secretary for health and director of the office of disease prevention and health promotion, a position he has held since 2012.

The change in leadership may slow down some of the activities under HHS' purview that concern biopharma. One of the more anticipated actions is an executive order relating to prescription drug costs. A draft version of the order that made the rounds among policy circles in June indicated the Administration would pursue mainly biopharma-industry policies in addressing high drug costs. *(Also see "Trump Exec Order On Drug Costs: Seeking To Balance Access, Innovation" - Pink Sheet, 23 Jun, 2017.)*

The order focused on policies in three broad areas: 1) the impact of insurance benefit designs on the net cost of drugs to the patient, 2) increasing competition in the market through faster approvals and 3) reducing regulatory burdens. It did not include any mention of government price controls.

The order also directs HHS and other government agencies, in consultation with stakeholders, to conduct a review of overly burdensome prescription drug regulations and administrative actions that could be revised or withdrawn, in keeping with the Administration's focus on de-regulation.

HHS under Price has welcomed input from industry on key issues. FDA recently issued notices to stakeholders seeking input on how the agency could reduce regulatory burdens. *(Also see "FDA Soliciting Broad Range Of Comments From Industry On Regulatory Reform" - Pink Sheet, 7 Sep, 2017.)* And Price held a series of listening sessions with stakeholders in the spring to help inform HHS policy on drug pricing. *(Also see "HHS Action On Drug Pricing: Here's Who Secretary Price Is Listening To" - Pink Sheet, 25 May, 2017.)*

*Former HHS Secretary Tom Price*

*Acting HHS Secretary Don Wright*

FDA has actively pursued policies aimed at lowering drug costs by increasing competition under Commissioner Scott Gottlieb, who has focused on speeding generic approvals and streamlining innovator development – as well as a host of more prominent, politically-sensitive topics including opioids and disaster relief.

At the Centers for Medicare and Medicaid Services, Administrator Seema Verma is planning to redirect the focus of the Cen-

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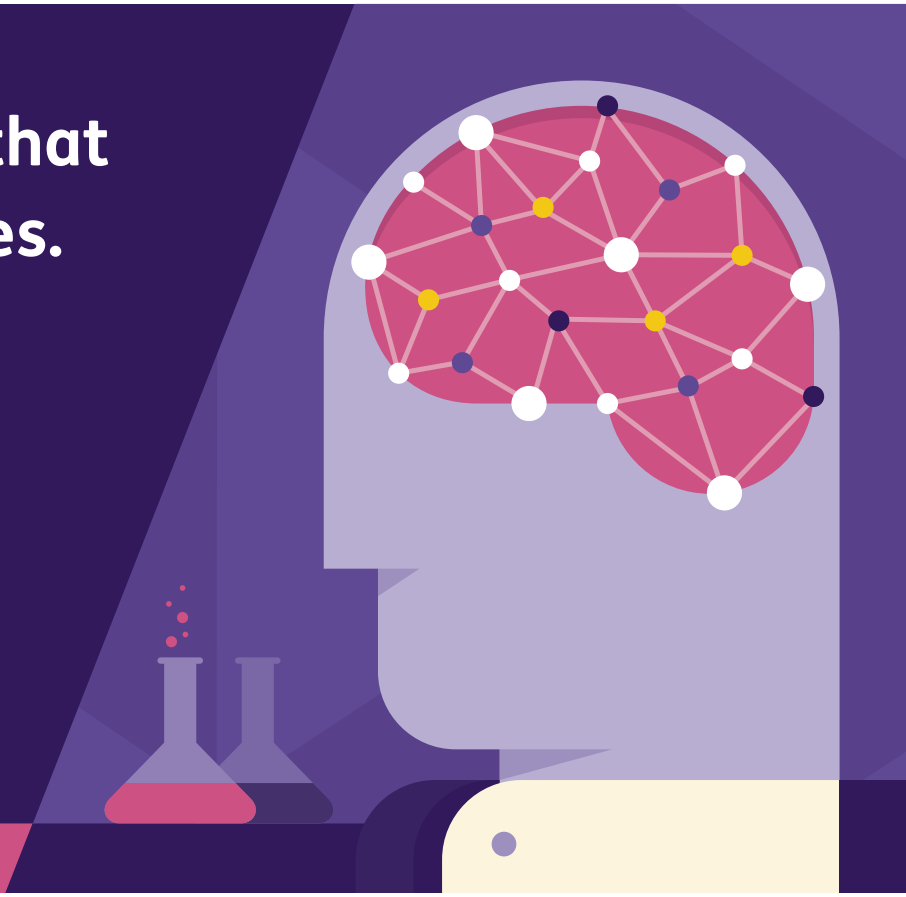

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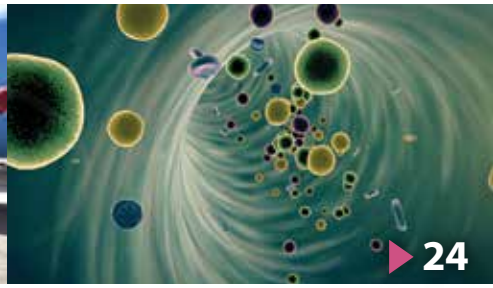


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ter for Medicare and Medicaid Innovation (CMMI) in a way that reflects the criticisms Price has leveled at Medicare payment experiments initiated by CMMI under the Obama Administration.

As part of that effort, CMS released a request for information Sept. 20 announcing that prescription drugs will be one area of focus for future payment experiments. *(Also see "Drug Payment Experiments Coming To Medicare, Medicaid" - Pink Sheet, 20 Sep, 2017.)*

Stakeholders are anxiously watching for a proposed rule on Medicare Part D from CMS. Agency officials have not spoken publicly about the proposal, which has prompted widespread speculation about what it will contain. *(Also see "CMS Proposal On Part D May Address Drug Costs, But Will It Target Prices?" - Pink Sheet, 31 Aug, 2017.)*

CMS is also considering a precedent-setting request from the state of Massachusetts seeking permission to use a closed formulary in its Medicaid program to drive down drug costs. Medicaid programs are currently barred from excluding drugs from coverage as long and manufacturers provide the statutory drug rebates.

The Administration did not announce plans for a permanent successor to Price. However, if the past is a guide, the future nominee is likely to be a politician – several former secretaries have been governors or members of Congress. With Wright appearing to be basically a caretaker, Gottlieb and Verma could take on more prominence in their roles until a new HHS secretary is confirmed.

Meanwhile, other key leadership positions at HHS also need to be filled. President Trump has nominated ViraCyte President and CEO Brett Giroir to become HHS Assistant Secretary for Health (the post Wright had been acting in before becoming acting secretary) and the nomination is awaiting confirmation in the Senate. Democrats have delayed approving the appointment because of comments Giroir made regarding defunding Planned Parenthood during his confirmation hearing before the Senate Health, Education, Labor and Pensions Committee.

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# Front-Runners Emerge In Race For EMA

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Shutterstock: Cheryl Ann Quigley

The European Commission has published its assessment of the 19 bids submitted by EU member states to host the European Medicines Agency when the much sought-after organization is forced out of London by Brexit in 2019.

The assessment, which will be used by member states when they vote on the new location in November, does not rank the bids in any order of preference. However, taken together with a recent EMA internal survey and a letter from LGBT staff citing concerns over the protection of their rights in certain member states, it looks as if the front-runners could include the Netherlands (Amsterdam), Spain (Barcelona), Denmark (Copenhagen), Italy (Milan), and Austria (Vienna).

Spain's chances of hosting the EMA will surely not be helped by the current political unrest in the northeast region of Catalonia, of which Barcelona is the capital. Images and scenes of police aggression against people attempting to vote in an independence referendum on Oct. 1 that the government in Madrid had declared unconstitutional were widely broadcast yesterday.

In the middle of the rankings are thought to be countries such as France (Lille), Portugal (Porto), Germany (Bonn), Ireland (Dublin) and Sweden (Stockholm), while eastern European member states like Bulgaria (Sofia), Romania (Bucharest) and Slovakia (Bratislava) are expected to come towards the bottom of the rankings.

The Commission's assessment, which was published and forwarded to the European Council on Sept. 30, shows the extent to which each of the 19 bids is considered to meet six criteria: suitable premises; accessibility; education facilities for families of staff; access to the labor market, social security and medical care; business continuity at the agency; and geographical spread of EU agencies.

Among the key criteria for the EMA are having appropriate, well-fitted out premises, and being able to ensure business continuity during and after the move. The latter criterion is highly dependent on the agency's ability to retain as many of its current staff as possible, which will be influenced by the desirability of the location itself, which will take account of criteria like the availability of places in nurseries, schools and universities, access to medical care and social security systems, and job prospects for spouses and partners.

An internal EMA survey among staff



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> Being able to ensure business continuity during and after the move will be highly dependent on the EMA's ability to retain as many of its current staff as possible.

based on these criteria saw the candidate cities fall into four main groups. Most staff would agree to move to one of the five countries in the first group, while the agency said that a move to the least favored country in the fourth group (eight member states) could see the agency lose 94% of its staff. *(Also see "EMA Paints Nightmare Scenario Of EU System 'Unraveling' If Relocation Goes Wrong" - Pink Sheet, 26 Sep, 2017.)*

The issue of staff concerns over the relocation are reflected in a report by Charles River Associates, commissioned by the European pharma industry federation EFPIA. Among other things, the report said that "the EMA's ability to retain or attract highly competent staff and internal subject matter experts to manage the central regulatory system is the primary factor in assessing the potential for disruption."

EFPIA issued a press release relating to an article about the CRA report by the Politico news service, which suggested the report ranked the 19 countries in order of preference, with Amsterdam the favorite. The study "looks across the spectrum of activities undertaken by the EMA and considers the impact of the move on continuity, on patients and on the approval of new medicines. The version of the report obtained by Politico also contained an analysis of the potential host city bids," EFPIA said.

EFPIA said the analysis "was not designed to produce a ranking of host cities and relative importance of each criteria was not evaluated. Contrary to the headline in Politico, the aim of the analysis is not to rank cities." The decision on the location of the agency is a matter for the member states, the group said, stressing that it was "critical" that the decision was based on objective criteria that support the continuity of the agency's functions.

## THE COMMISSION'S ASSESSMENT

Amsterdam is indeed considered to be in with a good chance of winning the race for the EMA. According to the commission's assessment, the Dutch capital has offered the 31,855sq m Vivaldi Building which will be "built to meet EMA's requirements." The building would be ready by April 1, 2019, although the Dutch offer doesn't give information on the issue of on-site archive, physical security and IT systems. A transition plan allowing the agency to remain operational would include the availability of a temporary backup building in addition to permanent premises and reinforcement of the Dutch Medicines Evaluation Board in order to assist the EMA. The government says it would provide pre- and post-location services to current staff to encourage them to move with the agency as well as to potential new recruits from the Dutch life sciences sector. Families of staff would be able to benefit from English-speaking nurseries and pre-school facilities, although the government does not provide specific information on the availability of places.

> Copenhagen has been very active in promoting its offer for the EMA.

Barcelona offers the 30,000sq m Torre Glories building, which according to Spain fulfils the EMA's requirements in terms of offices, meeting and conference facilities, archiving, and physical and IT security and standards. This building would be ready for occupation as early as the end of 2018. A "personalised service" would be offered to spouses and children of EMA staff "aiming at their rapid integration into the Catalan labour market." Barcelona also has "multilingual nurseries, primary and secondary schools as well as universities and business schools for children of EMA staff," says the offer, although "without providing specific information on their linguistic offer." There would be a "steering group" responsible for ensuring business continuity and the Spanish medicines agency, the AEMPS, intends to provide staff and services to EMA during the transition period.

One of the most active cities in terms of promoting its offer has been the Danish capital Copenhagen. The EMA would move into the 27,000sq m Copenhagen Towers, which the government says meets all EMA premise requirements, as of January 2019. Included in the offer is a plan to ensure a smooth transition to the new location, activities that Denmark plans to help the EMA recruit new staff, and a specific service for employees and their families to help the agency retain existing staff. Denmark's offer says children and spouses will have access to medical care but does not provide information on their access to social security, although it will offer a tailormade service to spouses on job research and opportunities. The city would provide day care and schooling facilities for all children of EMA staff, and the bid notes the availability of a European school and international private schools as well as university and higher-level educational facilities.

Vienna offers two main buildings – the 30,000sq m Austria campus and the 26,600sq m VIE 26 Erdberger Lände – and a third alternative, the 27,000sq m HoHo Seeparkcampus Ost. The government says Austria campus can fulfil all the EMA's requirements as regards meeting rooms and conference facilities, lounges and a conference center, but, according to the commission, the offer does not indicate the availability of work stations, a reception area, archives, physical security and IT standards. A phased relocation plan is put forward, but it does not say how it would help the EMA maintain current staff or keep the agency operational during the transition; it does though say settling-in support services will be available free of charge for staff and families. Access to medical care in Austria is "unrestricted" but the bid document does not provide information on access to social security, or on the availability of job opportunities in Vienna, although it offers a program to allow staff and families "rapid integration into the Austrian labour mar-

Four eastern European nations – Bulgaria, Romania, Slovakia and Croatia – lack an EU agency and will make much of this when pressing their case.

ket." As for educational facilities, there are kindergartens and international schools, as well as pre-schools and primary schools.

Milan, Italy's second-largest city, would offer the 50,260sq m Pirelli Building which it says "will be adapted to meet all EMA's requirements", although does not give information on telecoms network, data storage and data centers. Its plan would see the "smooth and effective" transition to the new relocation, with the moving of EMA resources completed by the end of January 2019. Spouses and children would have access to social security and medical care, and would also be offered "wide-ranging" assistance children and access to social security and medical care. However, the Italian government "does not provide information on the ability for EMA to maintain and attract highly qualified staff from relevant sectors," the commission observes.

## NOT SO FAVORED

At the other end of the scale, the Bulgarian capital Sofia offers proposed premises for the EMA by Jan. 1, 2019 at the latest, but the commission says the offer "does not indicate how these premises fulfil EMA requirements." Bulgaria provides no information on the timeframe for ensuring business continuity or on how the agency would retain staff, or on how the EMA would remain operational during the transition. There is information on various Bulgarian- and foreign-language (French and German) nurseries and schools but not on the availability of places. There are plans to establish a European school but no specific timing is given.

In the case of Romania, Bucharest has the 27,000sq m Globalworth Campus that it says would meet EMA requirements in terms of auditorium, archiving, physical and IT security and standards. A relocation timeplan on the construction and fit-out of the building is included in the offer, as well as a business continuity plan including measures for retaining EMA staff and the availability of skilled people from the national medicines agency and universities. Relocation support services would be offered for EMA activities, experts and their families, while children and spouses would have access to medical care and social security, as well as various primary and secondary schools with teaching in various languages.

Bratislava, the Slovakian capital, has proposed the Westend Plaza which it says meets most EMA requirements, although it does not mention off-site archiving and data storage networks. A relocation plan covers the construction and fit-out of the building as well as the relocation of EMA, "starting with preparatory steps in Q3/2017 and ending with a grand opening of EMA in Slovakia in January 2019." Slovakia would motivate EMA staff to relocate to Bratislava by providing "relocation assistance, benefits and special conditions," provide additional resources to its national institutes to support the EMA, and provide support programs and financial assistance to EMA staff and their families to prepare for the relocation. The offer mentions the various educational facilities available but without going into detail on the number of places that would be available. No information is provided on access to social security or medical care.

## GEOGRAPHICAL SPREAD, RENTAL COSTS

It remains to be seen how far the criterion of "geographical spread" of EU agencies is taken into account. All the five presumed front-runners have at least one agency already. Austria has one and Denmark has two. Italy also has two, including the European Food Safety Authority, as does the Netherlands, including the European Police Office. Spain has three, including the EU Intellectual Property Office. Most other bidding countries have at least one agency; France has three, and Germany, Greece and Portugal all have two.

Sweden hosts one key agency in the healthcare area: the European Centre for Disease Prevention and Control (ECDC) in Stockholm, while one eastern European candidate, Poland (Warsaw), has the Frontex border and coastguard agency.

By contrast, four eastern European nations – Bulgaria, Romania, Slovakia and Croatia – lack an EU agency, and they will be making much of this in pressing their case when the member states begin the decision-making process. Much behind-the-scenes jostling and bargaining can be expected. *(Also see "Avoid 'Political Games' Or Risk EMA Losing Most Of Its Staff, Italian Industry Head Warns" - Pink Sheet, 5 Sep, 2017.)*

Another factor that may help sway the decision one way or another is the terms for renting the EMA's new premises. Mindful presumably of the fact that EMA has no get-out clause regarding its current premises in Canary Wharf and may end up with an unpaid property bill of almost €350m, the agency will have favorable rental terms high on its wishlist. *(Also see "EMA And Brexit: Rental Liabilities Could Add €350m To Relocation Costs" - Pink Sheet, 28 Apr, 2017.)*

Austria's offer is the most generous in that it would rent the premises to the EMA for €1 per year for 25 years. Denmark would pay rent and charges for 20 years.

Other offers are not so generous. Slovakia would grant the agency a rent-free period of two years and cover fit-out costs, while Bulgaria would pay the first year's rent. Italy would cover all costs arising from the adaptation of the Pirelli building to ensure that it meets the EMA's requirements, and would charge the EMA nothing for 2019, but thereafter the rent would rise to the final price of €7m a year by 2022.

Portugal, which has proposed three different premises, would charge €16-18 per sq m including management and maintenance services, with one year's free rent, and Sweden would meet the rental costs for the first three years.

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# FDA Focusing On Drug Shortage Risks From Puerto Rico Hurricane

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*Federal delegation arrives in Puerto Rico*

The sun had not yet risen on the ninth day after Hurricane Maria struck Puerto Rico and took out the island's electrical grid when FDA Commissioner Scott Gottlieb boarded an Air Force jet at Andrews Air Force Base as part of a delegation of high-level federal officials.

The delegation headed by Elaine Duke, the acting Homeland Security secretary, would reconnoiter the island with Puerto Rico Gov. Ricardo Rossello and offer reassurance regarding the federal response to the still-unfolding disaster spawned by the Sept. 20 hurricane.

Aside from Gottlieb, the group included Transportation Security Administrator David Pekoske, U.S. Coast Guard Vice Admiral Karl Schultz and Rep. Jenniffer Gonzalez- Colon, R-Puerto Rico.

There was a press conference in San Juan where Duke said she would not be satisfied "until every Puerto Rican is back home, the power is back on, clean water is freely available, schools and hospitals are fully open."

Gottlieb had his own objectives in Puerto Rico: meet with FDA's team in San Juan for a damage assessment, visit FDA-regulated facilities to see some of the damage first-hand, and prepare to avert drug shortages.

He also brought agency staff some critical communications supplies and other equipment. FDA was still working to establish contact with agency employees in parts of the island that had severe communications challenges.

## LOOMING QUESTIONS

Television crews were broadcasting the humanitarian crisis facing the people of Puerto Rico – the search for food, water, shelter, gasoline for power generators and service for cell phones.

But beyond the island's immediate challenges, there was an emerging possibility of drug shortages in the US and perhaps other markets as a result of the hurricane.

There were still many questions about the great concentration of pharmaceutical plants in Puerto Rico, where 12 of the top 20 pharmaceutical companies have manufacturing operations. How had their workers fared? How badly were the facilities damaged? What could they accomplish with backup generators? When would their power be restored? And most importantly, what will it mean for the continued supply of critical drugs to the US and other countries?

## A KEY TO RECOVERY

There are deeper questions as well about the role of the pharmaceutical sector in Puerto Rico.

Attracted by federal tax incentives in the 1980s and 1990s, the industry forms the core of the US territory's economy. But there has been a long, slow economic decline since the key incentive in section 936 of the US tax code was finally phased out in 2006.

As Puerto Rico's tax base subsequently dwindled, its government became mired in debt. In May of this year, the territorial government obtained protection from creditors through a form of bankruptcy. Then came the blow from Hurricane Irma, followed by a direct hit from Maria.

Gottlieb delivered a reminder in a Sept. 25 statement on what's at stake with the hurricane recovery: "The island is home to a substantial base of manufacturing for critical medical products that supply the entire world. This industrial base is an important source of jobs and economic vitality for the island. It is a key to Puerto Rico's economic recovery. The manufacturing facilities are also a pivotal source of critical medical products for the entire United States. Helping to bring these resources back in operation is an important goal of ours and of Puerto Rico's."

## THE SPECTER OF DRUG SHORTAGES

FDA acknowledged in a Sept. 28 notice the possibility of drug shortages resulting from Hurricane Maria.

The agency said its working with the Health and Human Services Department, the Department of Homeland Security and local agencies "to find solutions to help prevent or limit any potential drug shortages that may or may not be directly related to the hurricane impacts."

FDA said it has identified more than 40 high-priority drug products made in Puerto Rico, the continued availability of which is essential.

The agency said it was working with at least five companies that were affected by the hurricane to prevent critical shortages of medical products in Puerto Rico and across the US.

"Assistance includes coordinating transport of certain critical drugs out of Puerto Rico," the agency said.

FDA added that the number of companies requiring assistance to prevent drug shortages could increase in coming weeks.


Photo credit: FDA

*Commissioner Gottlieb meets with San Juan staff*

> Since Sept. 22, "we have undertaken swift and extensive efforts to prevent or limit the loss or shortage of multiple drugs critical to American patients due to the challenges related to refrigeration, storage and transportation."

## THE HURRICANE SHORTAGES TASK FORCE

In a Sept. 25 statement, Gottlieb said that since Sept. 22, "we have undertaken swift and extensive efforts to prevent or limit the loss or shortage of multiple drugs critical to American patients due to the challenges related to refrigeration, storage and transportation."

He thanked officials at FDA, HHS, DHS and local agencies "for their commitment to finding a solution that would help avoid catastrophic drug shortages. This critical work included clearing debris to reach facilities; assessing fuel needs to keep generators running; and securing permissions to allow planes to land in Puerto Rico and fly critical products to the continental United States."

He noted that the agency is aware of several instances of potentially critical shortages "if we don't find a path for removal or ways to get production back up and running."

To address these challenges, he directed the agency to form a hurricane shortages task force. FDA also broadened the mandate of its emergency operations team to work on setting priorities for addressing potential medical product shortages.

## POWER RESTORATION EFFORTS

It appears that substantial progress with power restoration is likely during the next weeks and months.

The Energy Department said Sept. 29 that 95% of customers were without power.

Puerto Rico Electric Power Authority CEO Ricardo Ramos told CNBC Sept. 29 that 80% of transmission and distribution lines are down.

He said the less damaged, more accessible half of the island's electrical grid could be restored in two or three months.

Meanwhile, the Federal Emergency Management Agency said Sept. 28 that federal authorities are providing generators that are putting dialysis centers and drinking water systems back online.

However, FEMA said, "long-term power restoration will involve rebuilding generation, transmission and distribution capability."

FEMA said a power task force with representatives of the US Energy Department, the US Army Corps of Engineers, the private sector and the government of Puerto Rico "is working aggressively to develop a holistic plan to assess damage, build power resources, and restore power to the grid."

Energy Department emergency responders are working to restore power on the island to hospitals, airports, seaports, water treatment plants and communications facilities.

Meanwhile, Army Corps power response teams are assessing power needs and installing generators at critical facilities in Puerto Rico. They're transporting 300 FEMA and Defense Logistics Agency generators from the mainland.

The Navy, the Coast Guard and the Defense Logistics Agency are coordinating with the private sector to transport fuel to the island.

It is unclear, however, how much of this power restoration effort is directed at the pharmaceutical manufacturing facilities that are scattered around the island.

## COMPANIES RAMP UP EFFORTS

Pharmaceutical manufacturers operating on the island told the Pink Sheet their top priority is to ensure the safety of employees and their families. They have pledged millions of dollars to support relief and rebuilding efforts, and have activated employee assistance programs. Companies who responded to inquiries also provided some information about the status of their manufacturing facilities in Puerto Rico.

**Eli Lilly & Co.** told the Pink Sheet it has an affiliate, two manufacturing sites and a small sales force in Puerto Rico. As of Sept. 28, the company had accounted for almost 95% of its more than 1,100 employees in Puerto Rico and many of them reported to work over the prior week. "Our manufacturing sites had minimal damage, and the damage is not expected to hinder our operations as infrastructure begins to recover," Lilly said.

"Our inventory strategy for products is designed to protect against this type of event and we see no product supply risk to global markets at this time." The affiliate also sustained minimal damage, and is providing temporary shelter for some employees.

"We will continue to evaluate the state of the island's utility and transportation infrastructure as well as the situation of our employees when determining when to re-start production at our sites. No specific decisions have been made at this time," Lilly said.

**Amgen Inc.** said in a Sept. 25 statement that outreach to more than 2,000 workers and their families is ongoing. Amgen's facilities appear to have weathered the storm well. "The company's prelimi-


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nary assessment is that the critical manufacturing areas in our facility in Juncos, Puerto Rico, have not been significantly impacted by this storm," said Esteban Santos, executive vice president of Operations at Amgen.

Amgen said it is powering the site with backup generators, "and is working diligently with hundreds of its staff onsite to return its operations in Puerto Rico to normal as quickly as possible."

**Pfizer Inc.** told the Pink Sheet Sept. 28 that the company has completed a preliminary damage assessment of its manufacturing sites in Puerto Rico. Two received minimal damage, while the third had "minimal to moderate damage to parts of the facility." Pfizer added that "we are working to repair the facilities as soon as possible."

**Merck & Co. Inc.** told the Pink Sheet that the company is "still evaluating the potential impact on our operations in the US territory."

**Bristol-Myers Squibb Co.** told the Pink Sheet the company is "executing contingency plans that we believe mitigates product supply risk as we assess the situation on the island and work to bring our operations back online."

### SUPPLY CHAIN RISKS

The British Standards Institution warned clients in a Sept. 20 business intelligence memo of an increased risk of cargo theft or diversion in Hurricane Maria's aftermath.

BSI said its SCREEN supply chain intelligence network indicates that Hurricane Maria's impact on Puerto Rico and neighboring Caribbean islands "will likely significantly threaten the continuity of pharmaceutical supply chains and broader business operations in the region."

Even after authorities reopen the island's largest air freight hub in San Juan and after the US Coast Guard reopens Puerto Rico's seaports, regional commercial trade was unlikely to resume immediately, BSI said, adding that the authorities would instead give priority to disaster aid and security and emergency response forces.

"Due to these restrictions, cargo consignments may be diverted from their intended destinations to other facilities or held for extended periods of time at air or seaports," BSI said.

"These irregular shipping patterns expose goods to threats of tampering, theft, illicit diversion, and expiration, in the case of perishable products."

BSI added that ongoing public finance struggles have made recovery more difficult. For example, most routine maintenance of the government-operated electrical grid stopped for lack of funding after the territorial government filed for bankruptcy in May.

*From the editors of the Gold Sheet. Published online October 1, 2017*

*Editor's note: Brenda Sandburg and Derrick Gingery contributed to this report.*



# Complex ANDAs: Early Meetings With FDA Can Generate Bonus Communication

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Developers of complex generics will gain additional communication rewards if they follow FDA's formal meeting pathway.

Newly released guidance on formal meetings for complex product ANDAs outlines how and when product development, pre-submission, and mid-review cycle meetings are available. But it appears that the first two meeting types are keys to accessing the third, which could offer much more insight from FDA officials.

The new system is another step in what could be called the "new drug-ization" of the generic drug development process. FDA Commissioner Scott Gottlieb said in a blog post accompanying the Oct. 2 guidance release that the agency found from the new drug approval process that "early and better meetings between FDA and sponsors can improve development timelines."

*FDA outlines formal meeting process for sponsors of complex generic drugs.*

"We want to bring the same types of opportunities to developers of complex generics," he wrote.

FDA wants to communicate with sponsors early in development for these products, which historically have been difficult to approve, to facilitate a step-by-step journey and ensure the review takes as little time as possible.

Gottlieb said in comments during a workshop on modeling in generic drug development that the goal of the policies "is to make it more efficient, and in some cases, more feasible, to bring generic competition to these branded drugs."

Generic sponsors have complained that complex products have many hurdles that scare potential sponsors away. In GDUFA II, FDA committed to pre-submission meetings to help streamline development. *(Also see "Complex ANDAs To Be Allowed Pre-Submission Product Meetings" - Pink Sheet, 24 Oct, 2016.)*

Gottlieb has made increasing generic

competition in the hopes of lowering drug prices among his top priorities since taking office earlier this year. *(Also see "Gottlieb Places Drug Pricing Out Front In First Speech To US FDA Staff" - Pink Sheet, 16 May, 2017.)*

In conjunction with the meetings guidance, FDA also issued a scientific guidance on ANDAs for certain highly purified synthetic peptide drugs with rDNA reference products, as well as documents on ANDA amendments and refuse-to-receive standards (*see box*).

## ONE PRODUCT DEVELOPMENT MEETING REQUEST PER YEAR, PER PRODUCT

ANDA product development meetings are intended to allow for discussion between the sponsor and FDA officials about specific scientific issues or questions, such as proposed study designs, alternative approaches, or additional study expectations.

FDA wrote in the draft guidance that it expects the sponsor to have enough knowledge of the product to allow the agency to provide feedback to advance development.

Product development meetings will be granted for complex generics if FDA decides no product-specific guidance or "an alternative equivalence evaluation" for a complex product for which FDA has issued a product-specific guidance has been issued. The meeting may be granted if it concerns other complex product development issues, depending on available resources, according to the guidance.

Sponsors should not submit more than one product development meeting request per year, per product.

Pre-submission meetings are intended to occur about six months prior to ANDA submission and are intended to allow the sponsor to explain the content and format of the application. It will not include a substantive review of summary data or full study reports, but FDA will outline areas that need clarification before submission. The meeting also is not an opportunity to determine whether the ANDA will be acceptable for filing. Sponsors should not expect guidance on whether some required elements can be omitted, the agency wrote in the guidance.

FDA also said that pre-submission meetings may be requested no matter whether the sponsor had a product development meeting. Those who had a product development meeting or received written responses in lieu of such a meeting are not required to have a pre-submission meeting.

FDA said a sponsor that did not have a product development meeting also could be granted a pre-submission meeting, "if in FDA's judgment, the pre-submission meeting would improve review efficiency," according to the guidance.

Sponsors conducting one or both of those meetings appear to be the only ones eligible for a mid-review-cycle teleconference, where agency officials will discuss issues and possible deficiencies identified during the review. FDA wrote in the guidance that mid-cycle meetings will be held "with ANDA applicants that have participated in a prior product development or pre-submission meeting."

Mid-cycle meetings are only available during the ANDA's first review cycle. They are expected to occur 30 days after the mid-point of the review. Sponsors cannot request a mid-review cycle meeting. They are scheduled by FDA's regulatory project manager for the ANDA.

Product development and pre-submission meetings have formal goals for granting and scheduling. Mid-cycle meetings have no performance goals, in part because the date could change if the application is amended.

ANDA product development meetings are intended to allow for discussion between the sponsor and FDA officials about specific scientific issues or questions, such as proposed study designs, alternative approaches, or additional study expectations.

For sponsors, the opportunity to gain a peak into FDA's review before it ends should be compelling. It could inform launch planning or signal major corrections that will be needed following receipt of the complete response letter.

The formal meeting schedule is similar to that implemented for biosimilars after that user fee program launched in 2012. *(Also see "How To Get A Meeting With FDA: Guidance Describes Formal Meetings For Biosimilars" - Pink Sheet, 29 Mar, 2013.)*

NDA sponsors also enjoy a formal meeting schedule and in 2012 gained mid- and late-review cycle meetings to help increase first-cycle approvals. *(Also see "Buying Time: Industry Sacrifices Early To Gain Later With PDUFA V Review Model" - Pink Sheet, 1 Oct, 2012.)*

## MEETING PACKAGE WILL BE EXTENSIVE

Among the more difficult aspects of the formal meeting process for complex generic sponsors may be preparation of the meeting package, which is required when the request is sent.

FDA said in the guidance that the package should provide 11 items, including a brief

### NEW FDA GENERIC GUIDANCES

- ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin
- Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA
- ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA
- ANDA Submissions – Refuse-to-Receive Standards: Questions and Answers


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history of the development program and its current status and a statement summarizing the meeting purpose, as well as a proposed agenda and list of discussion questions "grouped by discipline as applicable with each question clearly numbered."

"For each question, there should be a brief explanation of the context and purpose of the question and any supporting rationale or data as applicable," the agency said in the guidance.

Data also should be at a level of detail "appropriate to the meeting type requested and the product development stage," FDA wrote.

Sponsors may give presentations during formal meetings, but FDA discouraged it in the guidance, saying that additional time will not be allowed for them. The agency also said sponsor presentations are not expected during mid-cycle meetings.

Sponsors continue to have problems with application quality, which could foreshadow problems gaining formal meetings under this requirement. During GDUFA I, agency officials reiterated that applications lacked necessary elements, causing additional review cycles. *(Also see "Generic Drug First-Cycle Approval Rates Lagging Under GDUFA I" - Pink Sheet, 25 Oct, 2016.)*

### MODELING ANOTHER AVAILABLE TOOL

FDA officials also indicated that modeling and quantitative methods already common in new drug development should be adopted by generics sponsors.

Office of Generics Drugs Director Kathleen Uhl told the workshop that the tools could be a transformative moment for generic drugs. She said they could optimize and streamline development for complex products and regulatory decision-making.

"This translates into numerous opportunities for more efficient development of drug products with limited generic competition, hence those in this complex drug space," she said.

The agency recently issued a list of drugs with no blocking patents or exclusivity that have no generic competition. *(Also see "FDA's Off-Patent, Off-Exclusivity List Draws Few Takers Early On" - Pink Sheet, 4 Aug, 2017.)*

*Published online October 2, 2017*

# FDA Rolls Out Zero-Tolerance Policy On ANDA Typos

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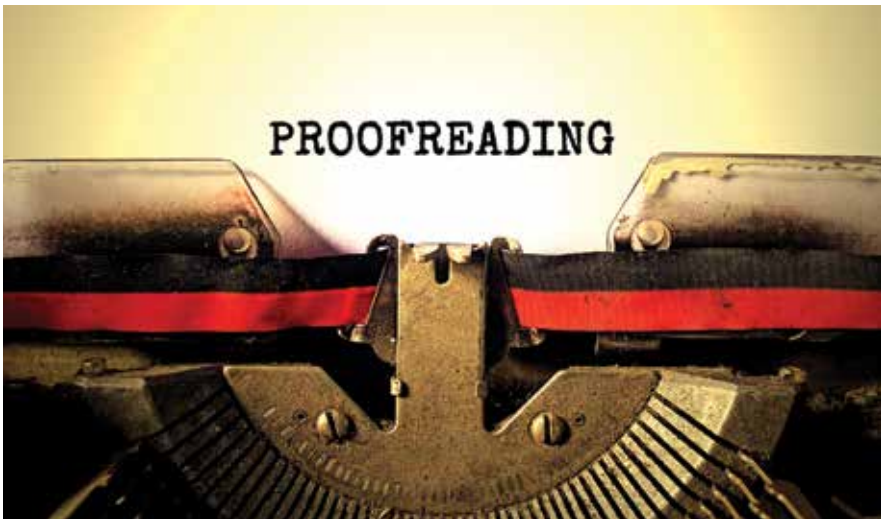


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Generic drug sponsors be forewarned: ensure the application is sufficiently proofread before it is filed.

The US FDA will not offer any sympathy for typos in ANDAs if they cause a major deficiency, such as a good manufacturing practice or quality control problem. The agency said in draft guidance that if it detects a major deficiency based on a typo and refuses to receive the application, it will not rescind the decision even if the sponsor acknowledges it and sends a corrected submission.

In a new question-and-answer document on ANDA refuse-to-receive standards, FDA gave another warning that application quality remains a top priority for its staff and should be for sponsors as well.

FDA wrote in the draft guidance released Oct. 2 that sponsors must ensure that "all relevant data and information necessary to support the substantive review is correctly transcribed into appropriate sections of the ANDA."

"When performing a filing review, the agency will assume that the information transcribed in an ANDA is correct," FDA said in the guidance. "The agency must move expeditiously through the filing process to ensure that FDA is able to meet its commitment to review and act on ANDAs within specified GDUFA performance metric goal dates."

Such a decision may seem like an unnecessarily harsh reaction to what would appear to be an innocent mistake. But it is another reminder that generic drug sponsors must pay close attention to their submissions, despite the focus on submitting them quickly. A refuse-to-receive action can mean losing first-to-file exclusivity.

Since the beginning of GDUFA I in 2012, FDA has complained that sponsors' application quality has not been adequate and lead to additional review cycles. *(Also see "GDUFA Success Depends On Industry Changes As Much As Review Improvements, FDA Says" - Pink Sheet, 4 Nov, 2013.)*

At the same time, FDA may be making more work for its reviewers. FDA wants to reduce the number of review cycles needed for approval. *(Also see "ANDA Reviews: First-Cycle Desired, But Two-Cycles OK?" - Pink Sheet, 27 Jul, 2015.)* More sponsors also could appeal RTR decisions. Appeals already have increased in part because sponsors feel decisions were not consistent. *(Also see "ANDA Refuse-to-Receive Challenges Become More*

*Common – And More Successful" - Pink Sheet, 20 Jul, 2015.)*

### SOME TYPOS AS MAJOR DEFICIENCIES APPEAR TOO LARGE TO DISMISS

FDA gave several examples in the guidance where typos leading to major deficiencies were not just numbers entered incorrectly. The agency said if a sponsor enters a date incorrectly for a stability study, which means it did not meet the recommended six-month minimum hold time, it will refuse to receive the application.

In another example, FDA said if a temperature, temperature range, or date do not confirm the proper storage conditions, even if in error, the application will be refused.

"A demonstration by the applicant that the basis of the RTR was caused by a typographical error will not be sufficient to rescind the RTR determination for this type of deficiency," FDA wrote in the guidance.

The statement implies that if the problem rises to the level of a major deficiency, it may be too severe for FDA to dismiss as a transcription error.

Indeed, given the data integrity problems FDA has found at some drug manufacturing facilities, the agency is paying close attention to the issue. *(Also see "Manufacturers' Data Integrity Problems Remain FDA Investigators' Focus" - Pink Sheet, 18 May, 2017.)*

FDA gave several examples in the guidance where typos leading to major deficiencies were not just numbers entered incorrectly.

Interestingly, the agency is more flexible when it comes to meeting requests. In another guidance on formal meetings for complex product ANDAs, the agency said requests will be denied "based on a substantive reason, not merely on the absence of a minor element of the meeting request or meeting package items."

Since GDUFA launched, the agency has allowed corrections to minor application problems without extending the goal date or forcing a complete response letter. *(Also see "FDA To ANDA Sponsors: Don't Forget Quality When Rushing For 10-Month Review Goal" - Pink Sheet, 17 May, 2016.)*

### OUT OF THE OFFICE? NOT FDA'S PROBLEM

FDA also will be uncompromising when it comes to contact information. The agency wrote in the guidance that if the point of contact listed in the ANDA is "out of the office," FDA will not search for a back-up contact person to send filling deficiencies.

FDA said its primary communication method for communicating deficiencies is secure email and that it is the sponsor's responsibility to ensure the point of contact is up-to-date.

"In the event that FDA receives an out-of-office message when communicating deficiencies by email to the point of contact, FDA will not contact any person not identified on Form FDA 356h," the agency said in the guidance.

Once FDA sends the filing deficiencies, the sponsor has seven days to make corrections or the application will be refused. FDA recommended that sponsors give a contact email address "that is checked regularly, even if the designated point of contact is out of the office, to ensure that all communications from FDA are received in a timely manner."

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# Copaxone 40mg Generic: FDA Exceeds Mylan's Expectations

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FDA beat **Mylan NV**'s expectations for the approval of its *Copaxone* generic, even though it appears that the agency may have missed the target date that had been set.

Mylan surprised investors late Oct. 3 when it announced the approval of its substitutable generic of **Teva Pharmaceutical Industries Ltd.**'s Copaxone (glatiramer acetate injection) for multiple sclerosis in 20 mg/mL and 40 mg/mL formulations. It was well before the company's prediction of approval in 2018 that had been given nearly two months ago.

The larger commercial opportunity should come from the 40 mg/mL formulation. Mylan said product launch is imminent, although no specific time was given. *(Also see " Surprise! Mylan's Copaxone Generic Sets Teva Up For A Struggle" – Pink Sheet, 4 Oct, 2017.)*

During its Aug. 9 earnings call, Mylan officials announced that they were adjusting guidance and expecting approvals of their generics for Copaxone and **GlaxoSmithKline PLC**'s *Advair Diskus* (fluticasone/salmeterol) in 2018, rather than 2017.

The frustrated executives said administrative problems at FDA, rather than scientific issues, were holding the applications back and that FDA's approval process remained unpredictable. *(Also see "Mylan Suggests Downside To FDA's Efforts To Improve Generic Drug Review" - Pink Sheet, 9 Aug, 2017.)*

Asked about the Copaxone generic's target date for approval during the call, Mylan President Rajiv Malik said that the latest date was mid-September, but he was


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hesitant to make it public. "I didn't put it out there because we just need to get to a place with FDA and have better understanding of that," he said at that time.

Mylan had submitted the application in mid-2014, before there were formal review goals for ANDAs, but FDA did create informal target action dates for many of those applications. If the date that Malik referenced was the target action date, it would appear that FDA was a couple weeks late. Mylan declined to comment on the review goal or why the product was approved ahead of the company's projected date.

The product is available in a 40 mg /mL three-times a week injection and 20 mg/mL once-daily injection. Mylan said in a press release that it was "one of the first applicants to submit a substantially complete ANDA" for the 40 mg/mL product containing Paragraph IV certification. As a result, the company could receive 180-day exclusivity, but no determination has been made, the company said.

**Sandoz Inc.** and **Momenta Pharmaceuticals Inc.** have partnered on an ANDA for a 40 mg/mL Copaxone generic, but it has been delayed by a quality issue at a contract manufacturer. *(Also see "Pfizer Warning Letter Trips Up Sandoz/Momenta's Expected Glatopa Launch" - Pink Sheet, 23 Feb, 2017.)*

## APPROVAL RIGHT AFTER FDA COMPLEX GENERIC POLICY ANNOUNCEMENT

Whether intended or coincidence, the approval came one day after FDA Commissioner Scott Gottlieb announced a new formal meeting system for complex generic product sponsors, intended to improve communication and speed approvals in a space where development historically has been difficult.

The agency created a product development meeting for sponsors to discuss scientific questions with FDA during the development stage, as well as pre-submission and mid-review cycle meetings.

The same day, the agency also issued a development guidance for highly purified synthetic peptide drugs using rDNA-based reference products. *(Also see "Complex ANDAs: Early Meetings With FDA Can Generate Bonus Communication" - Pink Sheet, 2 Oct, 2017.)*


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## PARTNER BONUS

Shares of Natco Pharma surged on Indian markets following news that partner Mylan had received FDA approval. Natco's shares, which were locked at the upper circuit, ended Oct. 4 at INR954.35 (+20%) on the Bombay Stock Exchange. Indian brokerage Edelweiss Securities was reported as saying that Natco could be entitled to 30% profit share from Mylan for the 20mg version and 50% for the 40mg product. Edelweiss said that it was expecting the launch of the 20mg/mL version in Q4 FY18 (January-March) with $11m revenues for Natco, but given a potentially earlier launch timeline, this could now be $25m -$30m in FY18 and around $55m in FY19.

It seems unlikely that FDA would choose this approval as an example of how it is streamlining complex ANDA reviews, given the public criticism it received from the sponsor during the review. The two events may simply be another illustration of the unpredictability of complex ANDA approvals that Mylan highlighted.

It's an unpredictability that FDA wants to eliminate. Since taking office earlier this year, Gottlieb has said that FDA should increase and streamline generic approvals to help lower drug prices. *(Also see "Gottlieb Places Drug Pricing Out Front In First Speech To US FDA Staff" - Pink Sheet, 16 May, 2017.)*

Increasing competition in the complex generics space is one area of focus. The agency recently issued a list of drugs with no blocking patents or exclusivity and no generic competition, in the hopes of spurring more interest. *(Also see "FDA's Off-Patent, Off-Exclusivity List Draws Few Takers Early On" - Pink Sheet, 4 Aug, 2017.)*

## PATENT DECISIONS REMAIN UNDER APPEAL

In January, a US district court determined four of Teva's patents on Copaxone were invalid, potentially clearing the way for generics to enter the market. *(Also see "Copaxone 40mg Generic At-Risk Launch Anticipated As Soon As February" - Pink Sheet, 31 Jan, 2017.)*

Teva said in an Oct. 4 statement that Mylan's launch should be considered at-risk. Teva said that it has planned for the eventual introduction of generic competition, but is confident in patient and physician loyalty to Copaxone. Teva added that it would continue promoting and supporting the product.

The company is appealing the district court ruling, as well as a December 2016 decision by the Patent Trial Appeal Board that nixed three Copaxone patents. *(Also see "Fate Of Copaxone 40mg Patents Depends On Courts After PTAB Rejection" - Pink Sheet, 13 Dec, 2016.)*

*Published online October 5, 2017*

# How to Avoid Data Integrity Disasters In Your Manufacturing Network

Pharmaceutical manufacturers can establish a competitive advantage by preventing questions about the integrity of their product quality data from disrupting current and future revenue, says Lachman Consultants.

In recent years, data integrity shortcomings identified during GMP inspections have cost firms dearly. In some cases, the financial impact has run into the hundreds of millions of dollars. Some of the effects are immediate, while others linger for years.

Despite the risk, many manufacturers generally do not seek help with data integrity compliance until after there's a problem, when it may be too late to avoid an impact on profitability.

For this reason, the Westbury, N.Y., consulting firm urges pharmaceutical companies to establish a competitive advantage simply by taking a proactive approach to data integrity assurance.

## A Secret Ingredient for Success

The problem of poor data integrity "isn't just about computers and it isn't just about non-US sites," Lachman's Jim Davidson explained in an interview.

Rather, he said, data integrity control is about revenues and growth. "Because it's the data that allows you to release product into the marketplace, and it's the data that gets you approval from regulatory agencies, it's fundamental to your ability to stay in business and to your ability to grow your business."

It's important for corporate executives to recognize the importance of data integrity to profitability, Davidson said. "You can't expect all CEOs of major companies to have an in-depth understanding of what's going on in some computer system in a lab somewhere, but they need to understand the impact it can have on their business."

## The Problem of Delayed Market Entry

The cost of remediating data integrity issues, while typically higher than that of preventing them, pales in comparison to the consequences in terms of delayed market entry.

When regulatory investigators inform a plant manager or senior quality executive that they no longer trust the integrity of the plant's quality data, there are certainly impacts on the plant's quality unit in terms of fixing the problem.

But once the agency's trust has been lost, other far more serious repercussions may come into play.

First, there is the question of whether the plant can continue distributing products with potential quality issues into the US market. If the plant is in another country, FDA can decide to add it to the agency's drug GMP import alert, immediately cutting off a revenue stream.

Second, there is the question of whether the agency will approve any pending new drug applications for drugs the company intends to manufacture at the facility.

It is not uncommon for serious data integrity findings to result in a suspension of such ANDA reviews until the problems are cleared up.

Third, the agency can respond to serious data integrity

problems by issuing a warning letter to the firm. Such letters warn of potential legal consequences and can undermine the confidence of customers, business partners and investors.

## The Problem of Close-Out Delays

Once sanctions have been imposed and a company begins the remediation process, a great deal of time can pass by before an FDA re-inspection of the facility can occur. As a result, a company's financial prospects can be significantly impaired due to delays in closing out warning letters, lifting import bans and approving applications.

Lachman estimates that, on average, it takes at least a year to resolve issues raised in a Form 483 report. Although there are cases where it has taken as little as six months, it frequently takes as much as two years. And when there is a warning letter, it can take even longer.

Unfortunately, during these delays, companies often must revise their revenue projections. They may find that during the hiatus, a first-to-file ANDA may have drifted back into a distant also-ran, which would translate into far less revenue potential for the firm.

Even after market removals due to warning letters or other regulatory deficiency notices are resolved, they can cast a long shadow over long-term future profitability, Lachman says.

The problem is that these developments constrain firms' strategic options. Because they're late to market, they must charge less. Meanwhile, they can face an increased cost of capital and reduced market capitalization. Plus, distrust among their employees and customers can make it harder to do business.

For these reasons, Lachman said in a recent whitepaper that data integrity issues "are fast becoming the biggest threat to profitability for the pharmaceutical manufacturer, particularly generics."

## The Real Cost of Poor Data Integrity

In a recent analysis, Lachman tallied the real cost of poor data integrity based on actual cases, and found that it was stunningly high.

In one case that Lachman researched, data integrity problems found on inspection led FDA to send a warning letter to a global manufacturer in January 2015, and ban US imports from two of its facilities in March of that year.

Exports, which had grown 39% over the previous four years, fell by $48 million.

Meanwhile, the firm spent an estimated $40 million to $70 million on remediation and write-downs.

Additionally, 41 generic drug applications and 38 drug master files were in jeopardy.

## A Billion-Dollar Fiasco

In another case, a large manufacturer based in India fared even worse, with a data integrity situation that Lachman figures will wind up costing it nearly a billion dollars.

This company's problems started with an FDA import alert in early 2013. Then the UK Medicines and Healthcare Products Regulatory Agency required the recall of multiple products, and in late 2013 FDA issued a second import alert covering all active pharmaceutical ingredients. The company recalled all products in 2015.

During this period, the firm's US revenues fell from 50% to just 24% of total revenues, for an expected revenue loss of $760 million.

Write-offs and remediation expenses in this case are expected to exceed $100 million.

Additionally, the firm saw a loss in market capitalization of $2.3 billion.

## A Painful Statistic

Given the high cost of poor data integrity, one might think that most of the world's thousand-plus generic drug firms would make sure they achieve sustained compliance in this area. But the reality is many do not, Lachman says in its whitepaper. "Our experience tells us that the number is painfully low."

Despite the benefits of the proactive approach to data integrity compliance, many firms don't seek help until they're already in trouble with the authorities.

That means they're in for a painful process.

"We'll come in with a team of people," Davidson said. The team will start going through data "to look at what impact the lack of controls has on the data itself for product in the marketplace, because that's what FDA is concerned about the most."

Lachman uses a statistical approach it has refined over the past few years to evaluate product lots that are already on the market, released based on data that have since become suspect.

It's an intrusive, disruptive process that consulting firms like Lachman will undertake to carry out these assessments, he said. It involves reviewing not just the electronic data but also the paper records for each batch.

If it's a firm outside the US, FDA may have imposed an import alert, Davidson said. "Now you can't export to the U.S. market anymore and if that was a big part of your business, that's a big loss."

However, the firm may still be trying to produce for the rest of the world, he said, "but you've got people like me and other consultants in your facility reviewing your data and interviewing your people in order to determine whether there are issues that impact the product's ability to remain on the market or not. This results in a need to commit significant internal time and human resources to support the independent data review."

## When Good Product Can Have Bad Data

Even if FDA finds a lack of data integrity, it doesn't automatically mean there's a quality or purity problem with the drug product.

For example, there have been cases where FDA found that laboratory technicians were weighing samples far more quickly than possible, revealed by reviewing weight tapes with time and date stamps, and concluded on this basis that they were likely replicating the same weight over and over again.

Although such a determination means the exact weight of the samples is unknown, "sometimes it doesn't end up impacting

the data in a meaningful way because the difference of that is a tenth of a milligram. But still, the data has been 'falsified.'"

It's up to the company, often with the help of outside consultants, to prove to the agency that there is no impact to the quality of the product. Davidson indicated that this can often be done by considering the totality of the data associated with a particular batch of product.

When Lachman responds to for-cause findings, "it's almost an emergency situation where you're trying to gather enough information to show that despite the issues uncovered by the regulatory investigator, the product in the market doesn't pose a risk to quality and efficacy of the products."

## Original Records Sin

Because the most highly publicized cases involve fraud allegations, many people have the mistaken impression that if their team is honest and ethical, they won't have a problem with data integrity. But such is not necessarily the case.

"Most people think it's fraud and in the overwhelming cases it's not," Davidson said. "There are instances where it is, but the overwhelming majority of the things we've investigated are data being compromised by sloppy practices and things of that sort."

It can result from poor systems design that stems from rapid growth. A company that starts out with one site and suddenly has five sites in several countries may not be prepared for the resulting management challenges. "The control piece can often get away from companies, and we certainly see that," Davidson said.

He noted that today's data integrity crisis echoes the US generic drug scandal of the late 1980s and early 1990s, when there would be what he calls "old school" data integrity failures. "One of the reasons for the keen interest by the regulators is they're intent on it not happening again."

Back then, firms were accused of fabricating records of equipment they didn't have, or substituting overcoated innovator tablets for bioequivalence testing.

But today's data integrity lapses differ, tending to revolve around computer records, and sometimes involving confusion about the regulatory guidance that has proliferated around this issue, Davidson said. "There are expectations out there in terms of guidance, but firms need to determine how best to implement the guidance procedurally at their firm."

*"In some parts of the world where the industry is growing very quickly there just aren't these mid-level or frontline manager and director-level people that are keeping track of what everybody is doing every day."*

*— Jim Davidson*

One area of confusion that often arises is around the concept of original records. People will print documents from an electronic system and treat them as original records like they used to do with paper-based systems. But they're not. "If there's a computer involved in generating the paper, then the electronic data that resides on the computer is the original data from the regulator's perspective," Davidson explained.

Some regulatory agency investigators have learned how to "go in and look at live data on … companies' systems and seeing what's there," Davidson said. "That's been a big change since 2013 when the recent trend of data integrity observations really began to get noticed."

## Crazy Quilt Guilt

Much of the focus of recent inspections has been on software in chromatography systems used for batch release testing.

The software in these testing systems uses a folder/file structure that's much like the one in Microsoft Windows computers.

As with any group of computer users, there will be a tendency in the analytical laboratory for each user to organize the file folders in shared equipment based on individual preference.

If "they're allowed to set up folders willy-nilly just any way they want and name them any way they want … and that happens a lot … the ability to go back in and find specific data becomes almost impossible."

Regulatory agency investigators will look in these chromatography systems during inspections, and "if they see a crazy quilt of folders in these systems … what happens is they don't bother digging around in those folders and proving that there's a data integrity issue. They just say that the conditions exist and are likely to cause a data integrity issue."

Then it's up to the firm to prove a negative, to show that the data are still intact as originally generated.

That can be straightforward with a well-organized file structure, but difficult if not impossible with a poorly controlled, poorly organized crazy quilt structure.

## The Importance of Data Governance

A key factor in ensuring data integrity is to establish a data integrity governance policy as discussed in regulatory guidance from MHRA, FDA and other regulatory authorities.

Putting this policy into place is more important at the outset than "worrying … about the detailed specifics of how I'm going

to do the things that are laid out in the data integrity guidance documents," Davidson said.

Once they have a data integrity governance policy, firms should develop the detailed procedures supporting the policy and periodically conduct internal audits to review compliance or rely on external auditing if they lack the expertise.

When firms have done this work up front and alerted FDA "that you've looked at the systems when they come in, you're looking at the systems, you're getting your house in order, and we've seen in some cases forbearance by the regulators."

When a firm has a plan with dates and commitments for addressing data integrity risks, regulatory authorities are more likely to let the firm continue with its own remediation.

"If you're in control of it yourself, it's a much easier thing than having to do it at the behest of the regulatory agency," Davidson observed.

## The Need to Hire the Right People

Right up there with establishing a data integrity governance policy is ensuring that the organization has people who can ensure that there are enough controls in place.

There is a tendency at firms to focus on strengthening data integrity by acquiring new information technology systems. But someone must know how to use them.

"We have worked with firms that bought IT data management systems that are the gold standard," Davidson said. "But then when they install them they don't install them properly."

Another personnel challenge that gets firms into trouble on data integrity is a shortage of managers.

"In some parts of the world where the industry is growing very quickly there just aren't these mid-level or frontline manager and director-level people that are keeping track of what everybody is doing every day."

When workers don't know how to do something, there's no one to ask. And when they don't realize they need to ask, there's no one who will see they need help.

"In places where they probably need it most there's the least number of those kinds of people to find and hire," Davidson said.

## The Perils of Password Sharing

Another issue is a tendency of workers to circumvent GMP controls, for example by sharing passwords to equipment such as analytical instruments.

A fundamental GMP requirement is to "attribute everything that's done to an individual and when they did it, when they took a particular action, did a specific operation, operated a certain instrument."

Even if the data generated with the equipment are good, sharing user names and passwords prevents the authentication required, Davidson said. "It's a GMP issue that leads to potential data integrity issues because you can't attribute the data to the person that actually did the work."

Plus, if the data are bad, password sharing makes the problem difficult to investigate. If you don't know who made the mistake, you can't ask them how it happened.

## Integrity Can't Be Outsourced

It's not unusual for FDA to find data integrity issues at firms that have been audited regularly by pharmaceutical companies that use them for contract manufacturing or testing.

The firms will often ask the consultant they've retained to deal with the issues FDA uncovered why their customers' auditors or their own internal or third party auditors didn't identify the problems. Davidson said that in many cases, the internal or external organizations that conduct these audits may lack sufficient expertise in terms of auditing to detect data integrity issues. In certain other cases, practices that put data integrity at risk are so deeply embedded (intentionally or unintentionally) in firms' systems that they are difficult to detect during a short term audit.

This is an important problem, because FDA and international regulatory authorities hold pharmaceutical companies responsible for the quality and data integrity of the work they outsource.

## The Need for a Holistic Approach

Although firms tend to focus on computer systems when troubleshooting data integrity issues, Davidson said Lachman takes a different approach. "We think it has to be done holistically."

"You have to look at how the computers and computer systems are being used by the people, the lab people or the manufacturing people that are actually touching them."

For example, workers can save production routines in tablet compression machines that govern factors such as speed. But if the company doesn't control access to that software, any worker could come along and change the routines.

In other cases, software limits the number of user name/password pairs a production machine will accept. If it allows 10 passwords but 30 workers need to use it, then there is going to be password sharing – and it will be impossible to tell who was using the production machine when a deviation from required practices occurs.

## A Better Way

In the end, those who view quality as an investment rather than a cost do best on data integrity, Lachman emphasizes in its white paper. "This requires a mindset shift away from being a victim of the winds of regulatory demands to proactively seeking the source of quality deficiencies."

Rather than brace for expensive surprises like recalls, import bans and loss of reputation, Davidson said it's so much better to incorporate activities like proactive data integrity focused auditing into your budget and schedule. Whether done internally or with the help of an outside firm, it can be so much more effective than waiting to find out what the regulator sees and hoping for the best.

Lachman
CONSULTANTS

# 'Promising' Status For Faron's Traumakine In UK Opens Possibilities For Early Access, Pricing Negotiations

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A PIM designation by the Medicines and Healthcare products Regulatory Agency is the first part of a two-step evaluation process for its Early Access to Medicines Scheme (EAMS).

Finnish biotech company **Faron Pharmaceuticals Oy** has received a "promising innovative medicine" (PIM) designation from the UK regulator for its lead product, *Traumakine* (FP-1201-lyo), in the treatment of acute respiratory distress syndrome.

ARDS is a severe orphan disease with a reported mortality rate of approximately 30-45%, for which there is currently no approved pharmacological treatment. Faron says Traumakine, recombinant human IFN beta-1a, can offer patients significant benefits over the current standard of care in terms of reduced mortality and morbidity as well as reducing time spent in intensive care units.

A PIM designation by the Medicines and Healthcare products Regulatory Agency is the first part of a two-step evaluation process for its Early Access to Medicines Scheme (EAMS). The MHRA scheme aims to give patients with life-threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorization when there is a clear unmet medical need.

Following the PIM designation, a company is expected to complete its clinical development program within a reasonable timeframe before it can continue towards the next stage of the EAMS process. This second stage involves the drug to being made available to patients earlier, and opens the door for early pricing negotiations with the UK health technology assessment body, the National Institute for Health and Care Excellence (NICE).

Faron says Traumakine is based on a patent-protected use of intravenous interferon beta to prevent leakage of vascular beds in acute lung injuries. The product is currently being tested in a Phase III trial (INTEREST) in approximately 60 hospitals across Belgium, Finland, France, Germany, Italy, Spain and UK. INTEREST is a double-blind, randomized, parallel-group comparison of efficacy and safety of interferon-beta and placebo in the treatment of patients with moderate to severe ARDS. The company expects to complete recruitment of the targeted 300 patients during the fourth quarter of 2017, a spokesperson told the *Pink Sheet*.

## SIGNIFICANT BENEFIT OVER CURRENT STANDARD OF CARE

At present, there is no approved pharmacological treatment for ARDS. The spokesperson explained that ARDS patients are at present generally treated with lung-protective mechanical ventilation, and this treatment is accompanied by ancillary support, such as positioning, fluid management, and food restrictions.

"Complications which can arise whilst a patient is being treated for ARDS include the development of other organ injuries, infections, pneumothorax, lung scarring and blood clots which can develop into a pulmonary embolism. These complications need to be addressed with separate treatment regimes," the spokesperson added.

The spokesperson explained that the primary efficacy endpoint in the INTEREST trial is the all-cause mortality rate at day 28, the only accepted primary endpoint for marketing approval by the European Medicines Agency. "The INTEREST trial protocol is targeting a 50% reduction in all-cause mortality at day 28 between placebo and treatment arm (from 30% to 15%)," the spokesperson said.

Faron said it was currently "focused on completing recruitment and delivering readout from the INTEREST trial" and could not comment on when it expected the drug to be licensed in the EU. Traumakine already holds an EU orphan drug designation, grant-

## PIM DESIGNATION DATA

From when the EAMS was launched in April 2014 to Sept. 20, 2017, the UK Medicines and Healthcare products Regulatory Agency has received **57 applications** for a PIM designation. Of these, **41** have been granted, **eight** have been refused, **two** have been withdrawn and **6** are pending.

*Source: MHRA*


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ed in November 2007.

In September, the company announced that it planned to initiate an expanded access program for Traumakine once the INTEREST trial in the EU is closed to new patients. Faron said this would allow compassionate use of Traumakine in eligible named patients at European ICU hospitals who may benefit from Traumakine treatment ahead of the product's potential regulatory approval. The company was also considering providing this access to ARDS patients in the US.

### REST OF THE WORLD

In addition to the pan-European INTEREST study, Faron's Japanese licensing partner, **Maruishi Pharmaceutical Co. Ltd.**, is conducting a Phase III study with Traumakine in Japan. The two Phase III trials combined aim to treat 420 moderate to severe ARDS patients in total.

In the US, the Food and Drug Administration has proposed that Faron can proceed directly to a biologics license application submission for Traumakine pending positive results from the two ongoing Phase III trials (INTEREST in Europe and MR11A8-2 in Japan).

"Subject to the FDA being satisfied with data from the trials, the BLA application for Traumakine can be filed purely with data obtained from the ongoing trials outside of the US. In the event of positive outcomes of the ongoing trials this FDA feedback is therefore expected to shorten the time for approval of Traumakine in US," the Faron spokesperson said.

Traumakine is also being investigated in a second indication for the prevention multi-organ failure and mortality among operated RAAA (Ruptured Abdominal Aortic Aneurysm) patients for which an additional European Phase II trial is underway.

*From the editors of Scrip Regulatory Affairs. Published online October 2, 2017*



# FDA's NDA And BLA Approvals: Fiasp, Ascor

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

| SPONSOR | PRODUCT | INDICATION | CODE | APPROVAL DATE |
|---|---|---|---|---|
| **New Drugs** | | | | |
| Novo Nordisk | *Fiasp* (insulin aspart injection) | Improved glycemic control in adults with diabetes mellitus. | S, 5 | 9/29/2017 |
| McGuff | *Ascor* (ascorbic acid injection) | Treatment of scurvy in adult and pediatric patients age 5 months and older for whom oral administration is not possible, insufficient or contraindicated. | S, 7 | 10/2/2017 |

| KEY TO ABBREVIATIONS | |
|---|---|
| **Review Classifications** | **NDA Submission Classification** |
| **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 |

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# Kevzara: Sanofi Caught In Middle Of US FDA Debate On Data Analysis

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When views on clinical or statistical issues evolve among US FDA staff, sponsors may find themselves caught in the middle of the agency's internal debate.

The second-cycle review of **Sanofi** and **Regeneron Pharmaceuticals Inc.**'s interleukin-6 receptor antagonist *Kevzara* (sarilumab) was complicated by a matter seemingly outside the companies' hands: a disagreement within FDA over how best to reflect radiographic progression clinical data in labeling for the rheumatoid arthritis (RA) treatment.

While reviewers from various disciplines all agreed that sarilumab had demonstrated efficacy on the radiographic progression endpoint in a 52-week pivotal trial (Study EFC11072), they disagreed over the statistical method that should be used in the analysis.

"There was no disagreement that the Study 11072 demonstrated that sarilumab decreased the progression of structural progression in patients with rheumatoid arthritis," Badrul Chowdhury, director of the Division of Pulmonary, Allergy and Rheumatology Products (DPARP), said in a May 22 review. "Rather there were differences in opinion whether the results should be displayed in the label using linear extrapolation method … or using alternate methods."

All three statistical methods under consideration – linear extrapolation, all available observed data, and linear mixed effects regression model – showed dose-dependent, statistically significant decreases in radiographic progression with sarilumab 200 mg and 150 mg compared to placebo, Chowdhury noted. However, all three methods had their limitations in how they treated data for patients who started in the placebo arm but switched over to active drug during trial.

The sarilumab review was marked by numerous agency internal discussions and information requests to sponsor Sanofi on this issue. In both the first- and second-cycle reviews, Sanofi reluctantly agreed to use of one of the alternative statistical methodologies for the sake of getting an on-time approval, even though it favored the linear extrapolation method that had been used for other RA development programs and was prespecified in the study protocol.

Such was the extent of disagreement internally within the statistical and clinical review teams at FDA, and between the agency and the sponsor, that the issue ultimately landed on the desk of Center for Drug Evaluation and Research (CDER) Director Janet Woodcock, who came down in favor of the sponsor's preferred linear extrapolation method.

Yet, use of this method in sarilumab's labeling should not be seen as a continued agency endorsement of this analytical approach, Office of Drug Evaluation II (ODE II) Director Curtis Rosebraugh said in a May 22 memo.

"This should not be viewed as a validation of this type of method over others but rather a practical acknowledgement that timely consideration and debate of new methods of evaluation is necessary when supplanting one that has been used for years and is typical of an evolutionary process," Rosebraugh said.

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> FDA's decision to go with the prespecified linear extrapolation approach is "a practical acknowledgement that timely consideration and debate of new methods of evaluation is necessary when supplanting one that has been used for years."
> – ODE II Director Rosebraugh

Whether or not to require a cardiovascular outcomes trial for sarilumab also garnered high-level attention within CDER.

## CROSSOVER DESIGN COMPLICATES ANALYSIS

FDA approved sarilumab May 22 for treatment of adults with moderately to severely active RA who have had an inadequate response or intolerance to one or more disease-modifying, antirheumatic drugs (DMARDs) *(Also see "Keeping Track: Immunology In Focus As US FDA Approves Kevzara, New Breakthrough Actemra Use; J&J, Sun Advance Psoriasis Candidates" - Pink Sheet, 29 May,*


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*2017.)* Approval was delayed by a first-cycle complete response letter resulting from manufacturing deficiencies at Sanofi's Le Train, France, fill-and-finish facility. *(Also see "Sanofi Working To Resolve GMP Issues That Derailed Sarilumab Approval" - Pink Sheet, 28 Oct, 2016.)*

The biologics license application was supported by two Phase III studies: EFC11072 Part B cohort 2 and EFC10832, both of which were double-blind, placebo-controlled trials in patients with moderately to severely active RA and which provided open-label rescue therapy for patients with inadequate response to double-blind treatment.

In EFC11072, RA patients were randomized to either of two sarilumab doses (150 mg or 200 mg) or placebo, on top of background methotrexate therapy, for 52 weeks. Patients in the placebo arm who did not achieve 20% or higher improvement in tender joint count and swollen joint count were allowed to cross over to the highest sarilumab dose starting at week 16.

The study included a radiographic assessment of structural damage progression based on change from baseline to week 52 in the van der Heijde modified Total Sharp Score (mTSS).

Although the study included escape provisions, the possibility that RA patients could remain on placebo for up to 52 weeks raised ethical concerns among agency staff during the review's second cycle.

The high rate of crossover from placebo to sarilumab complicated analysis of the radiographic progression data.

"At the primary time point of week 52, approximately 55% [of] patients from the placebo treatment arm had crossed over to the sarilumab treatment arm. At the earlier time point of week 24, approximately 45% [of] patients from the placebo treatment arm had crossed over to the sarilumab treatment arm," Chowdhury wrote in a May 18 second-cycle summary review.

Patients who crossed over and patients with missing data had their data imputed by linear extrapolation; radiographic data from baseline and the last available time point before crossover were used to fit a straight line to impute data for week 52.

Although this imputation method has been used historically in other RA programs, it has limitations "because data are imputed based on assumptions that the radiographic damage would progress in a linear fashion beyond the last available radiograph data," Chowdhury said.

## STATISTICIANS PREFER ALL OBSERVED DATA METHOD ...

During the BLA's first review cycle, FDA's statisticians objected to using the linear extrapolation method even though it has been used in other RA development programs and was the protocol-specified primary method for the study, Chowdhury said in a May 22 review.

The statistical team asked Sanofi to use an alternate method based on all available observed data, where data from patients in the placebo arm who crossed over to sarilumab would be counted toward the placebo arm, Chowdhury said. *(See reviewers chart, p. 22)*.

However, this method also has limitations, the DPARP director said.

"For the latter part of the study, when some placebo-treated patients have crossed over to sarilumab, the comparison is between the same treatments, sarilumab to sarilumab," Chowdhury said. "Since patients crossed over from placebo to sarilumab are on active treatment, radiographic progression is likely to be impacted and slowed; therefore, this method is likely to underestimate the true mTSS effect size."

In the first review cycle, Sanofi objected to using the all available observed data approach, Chowdhury said, although the sponsor agreed to do so prior to the original PDUFA action date.

In his May 22 summary basis for regulatory action, Rosebraugh noted that while all the methods have their strengths and weakness, "the linear extrapolation method has elements that the statistical group has been evolving beyond which brought this issue to the forefront."

"Initial consideration between stats and the sponsor around the use of all observed data occurred during the first review cycle, but were never formalized with all the review team as manufacturing deficiencies took precedence," he said.

After resolving the manufacturing deficiencies that led to the October 2016 complete response letter, Sanofi resubmitted the BLA in March 2017 for a two-month review and a May 22 user fee goal date.

## 3 STATISTICAL METHODS

1. **Linear Extrapolation** – Assumes that patients continue to have radiographic progression at the same linear rate as was observed throughout the time of escape/withdrawal. The primary concern from a clinical perspective is that this analysis method may overestimate true progression.
2. **All Available Observed Data** – X-ray data are analyzed according to randomized treatment group, regardless of treatment discontinuation or escape. This methodology is anticipated to be more conservative than assuming linear progression.
3. **Linear Mixed Effects Model** – Includes all radiographic data observed prior to escape, including data collected at any time point during the 52-week, double-blind period. In this method, placebo-treated patients who have crossed over to sarilumab contribute no data at week 52, which may underestimate the true effect size if the progression on placebo would have been on a progressive slope.

### ... BUT CLINICAL DIVISION NOT ON BOARD

The question of the most appropriate statistical methodology for presenting the radiographic progression data resurfaced again during the second review cycle, Chowdhury said in his May 22 memo. "I was reluctant to use the all available observed data method because in this method the missing placebo data are replaced by data from patients on sarilumab 200 mg, which seemed clinically not reasonable," he wrote.

A meeting to discuss the all observed data method was held April 22 between the clinical and statistical review teams and Rosebraugh, the ODE II director and signatory for the sarilumab application. "The office signatory expressed hesitancy with the all observed data method," Chowdhury said.

On May 4, the statistical team requested Sanofi perform an analysis using a linear mixed effects regression model that includes all radiographic data available prior to crossover (+14 days), including data collected at any time point during the 52-week, double-blind treatment period. This analysis includes all sarilumab data and all placebo data without crossover.

"This method also has limitations, perhaps less so than the previous two methods," Chowdhury said in his May 18 memo. "In this method, placebo-treated patients who have crossed over to sarilumab contribute no data at week 52, which may underestimate the true mTSS effect size if the progression on placebo would have been on a progressive slope."

In an internal follow-up meeting May 12, Rosebraugh tentatively considered the linear mixed effects regression method acceptable for presenting the radiographic progression data in labeling.

## Kevzara Reviewers

| | |
|---|---|
| **Medical** | Suzette Peng |
| **Chemistry** | Gerald Feldman (product quality); Laura Fontan (manufacturing facilities) |
| **Clinical Pharmacology** | Jianmeng Chen; Sheetal Agarwal; Anshu Marathe |
| **Microbiology** | Candace Gomez-Broughton (drug substance); Lakshmi-Narasimhan (drug product) |
| **Pharmacology/ Toxicology** | Eleni Salicru; Timothy Robison |
| **Statistics** | Yongman Kim; Thomas Permutt; Gregory Levin |
| **Cross-Discipline Team Leader** | Janet Maynard |
| **Regulatory Project Manager** | Christine Ford |

> The final decision to use the prespecified linear extrapolation method was made at the CDER center director level.

### SANOFI/REGENERON MAKE THEIR CASE FOR LINEAR EXTRAPOLATION

Revised labeling using the linear mixed effects regression method was sent to Sanofi. "The Sanofi team responded stating that their preference was to use the linear extrapolation method, but would consider alternate language," Chowdhury said. "Sanofi and their development partner Regeneron also emailed a correspondence 5/17/2017 (submitted to the BLA on 5/22/2017) and copied the center leadership."

However, Sanofi and Regeneron remained unhappy about this turn of events late in the review process.

"On Sanofi's request, a teleconference was held between leadership of Sanofi and Regeneron, and the clinical and statistical team of the FDA," Chowdhury said. "Sanofi and Regeneron's main argument was that the linear extrapolation method has been previously used in RA programs, and for Study 11072 the linear extrapolation method was pre-specified in the study protocol and agreed upon method with the agency at end-of-Phase II meeting and in the statistical analysis plan."

Sanofi and Regeneron asserted that the alternate methods "can be post-hoc sensitivity analyses, but should not be used as the primary analysis for display of results in the product label. Furthermore, Sanofi argued that these alternate methods have not been thoroughly vetted."

Nevertheless, the sponsor heard the user fee clock ticking. In a May 18 submission, "Sanofi stated that they would reluctantly agree to the linear mixed effects regression model to get to a timely action on the BLA."

Chowdhury's May 18 review suggests he favored the linear extrapolation method, in part because of FDA's historical approach to analyzing such data for RA therapies.

The mTSS effect size numerical differences for the three methods were not large, and all reached statistical significance in a dose-dependent manner, suggestive of the robustness of the treatment effect. "Nevertheless, it is important to apply the most reasonable statistical method, and apply it consistently across various drug development programs," Chowdhury said. "For other programs, if the treatment effect is not as robust, statistical methods may become important if the statistical significance is lost in one of these analyses."

In the case of sarilumab, it appears that approaches using all available observed data and linear mixed effects regression model may underestimate the true effect size, Chowdhury said. "For this sarilum-


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ab program, among the three methods, linear extrapolation method would be more reasonable to use since the radiographic progression using this method is higher for the placebo treatment arm than other methods. Furthermore, the linear extrapolation method was discussed and agreed upon at the end-of-Phase II meeting, delineated in the statistical analysis plan, and this method would be consistent with other biologic product labeling approved for RA."

However, he recognized that there may be hesitation in using imputed numbers, and "there may be some merit in the future in relying on linear mixed effects model or some other method that does not impute data."

In a May 18 review, the agency's statisticians continued to favor either the all observed data approach or the linear mixed effects model method over linear extrapolation.

"We have concerns with the reliability of results based on linear extrapolation because such results rely on strong and unverifiable scientific assumptions and the use of inappropriate statistical methodology, and more appropriate alternative statistical approaches are available," statistical reviewer Gregory Levin said.

## OND'S STEIN, CDER'S WOODCOCK GET INVOLVED

Although there was internal agency consensus on the linear mixed effects regression method, the issue had not been put entirely to rest.

Peter Stein, deputy director of the Office of New Drugs (OND), "got involved and discussed the radiographic progression analyses methods with the office director signatory of this BLA, the statistical division director, and myself," Chowdhury said.

Stein joined FDA in November from **Merck & Co. Inc.** *(Also see "Merck R&D Exec Jumps To US FDA As Office Of New Drugs Deputy Director" - Pink Sheet, 8 Nov, 2016.)* He arrived at the agency less than two months before longtime OND director John Jenkins retired in early January. *(Also see "Merck R&D Exec Jumps To US FDA As Office Of New Drugs Deputy Director" - Pink Sheet, 8 Nov, 2016.)*

Since Jenkins' departure, Woodcock has been serving as OND acting director while the agency searches for a permanent replacement.

> "It is important to apply the most reasonable statistical method, and apply it consistently across various drug development programs."
> – DPARP Director Chowdhury

**DRUG REVIEW PROFILE**

CLICK

Go online for a timeline of key steps in the Kevzara review, plus these additional articles in the Drug Review Profile:

- **CDER Safety Outcomes Trials Group Vetted Kevzara CV Study Need**
- **Ethics Of Kevzara's 52-Week Placebo Trial Weighed On US FDA**

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Jenkins, however, had raised concerns about Woodcock's plans to temporarily lead OND given what he viewed as the center director's appearance of bias in the review of **Sarepta Therapeutics Inc.**'s Duchenne muscular dystrophy drug *Exondys 51* (eteplirsen), which she approved over the review team's objections. *(Also see "Woodcock's 'Bias' In Sarepta Case Made Jenkins Worry About Future Drug Reviews" - Pink Sheet, 31 Jul, 2017.)*

The sarilumab review documents indicate Woodcock, a rheumatologist by training, also got involved in the statistical analysis debate.

"After consideration of various viewpoints, Dr. Stein conferred with the center director, and decided that the sarilumab product label would display the radiographic progression results using the prespecified linear extrapolation method," Chowdhury said. "This decision was made at the center director level."

In his May 22 memo, Rosebraugh acknowledged the " wide range of opinion" over how the sarilumab radiographic progression data should be shown in labeling. Discussion of linear mixed effects model "occurred rather late in the review cycle. This allowed for only limited internal discussion and limited discussion with the sponsor," he said.

"After conferring with upper management, it was decided, with agreement from [Division of Biometrics II Director Thomas Permutt] that for this particular application we would continue representing the results with linear extrapolation," Rosebraugh said.

Kevzara labeling on the data from Study EFC11072 reflects the mean change in mTSS and its components, the erosion score and joint space narrowing score, at week 52 using the linear extrapolation method to impute missing or post-rescue data. Sarilumab 150 mg and 200 mg doses were associated with significantly less radiographic progression of structural damage compared to placebo, with mean differences in mTSS of -1.88 for the 150 mg dose and -2.52 for the 200 mg dose.

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LET'S GET SOCIAL @PharmaPinksheet

# Mechanism-Based Drug Rejection? Ataluren's Unlikely Personalized Medicine Milestone

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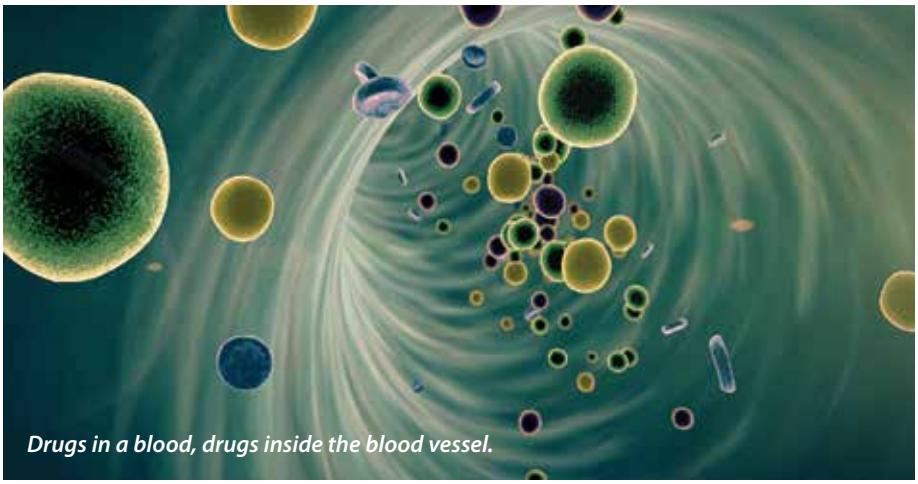

*Drugs in a blood, drugs inside the blood vessel.*

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US FDA has shown it can be very flexible in expanding indications for a targeted therapy with a clearly established mechanism of action. But, as PTC Therapeutics learned, the agency's willingness to apply mechanistic knowledge for targeted therapies cuts both ways.

Among the many innovative approaches the US FDA is applying to defining substantial evidence of efficacy, one of the most far reaching may be the move towards mechanism-based approvals.

In an era of personalized medicine and targeted therapies, it stands to reason: if you really understand the biological mechanism underlying a disease, and you design a drug to block or repair that target precisely, you should have a lot more confidence that it will work in humans before you ever give it to a single person.

FDA had already taken steps applying that principle in specific cases. Most notably, the agency has approved expanded uses for **Vertex Pharmaceuticals Inc.**' cystic fibrosis therapies despite less than stellar clinical results in some forms of the disease – and, in the case of a May 17 approval for *Kalydeco* (ivacaftor) for 23 especially rare variations of CF, based on no clinical data at all. *(Also see "Kalydeco Expands Indication Without Clinical Data; Keytruda Is Latest Bladder Cancer Approval" - Pink Sheet, 21 May, 2017.)*

FDA's rationale: *Kalydeco* was proven dramatically effective in its initial indication (the G551D mutation) so there is strong clinical evidence that it's mechanism of action (exon-skipping) works. That allows the agency to be more flexible on subsequent uses.

The idea was enshrined in Section 3012 of the 21st Century Cures Act, which explicitly authorizes FDA to base approvals of targeted therapies for rare diseases based on evidence of effectiveness for related indications. *(Also see "The Evolution Of 21st Century Cures Legislation" - Pink Sheet, 29 Nov, 2016.)*

We aren't at the point where FDA would approve a drug like *Kalydeco* based on the mechanism alone – but you can start to see the possibility of getting there from here.

There is, however, another side to the story, as **PTC Therapeutics Inc.** learned when it's proposed Duchenne Muscular Dystrophy drug ataluren went before the Peripheral & CNS Drugs Advisory Committee Sept. 28.

It turns out that, if clinical data from one indication can support a particular mechanism for approval in a different indication, then a failed trial in one disease can cast doubt on the mechanism in another setting.

To be clear, FDA had significant doubts about the efficacy of ataluren already, as evinced by two Refuse-to-File letters declaring that the existing clinical trials on their face did not show efficacy. And the advisory committee agreed that the existing data don't yet meet the bar for efficacy. *(Also see "Patients Can't Clear Translarna's Data Hurdles As PTC Falls Short At FDA Panel" - Pink Sheet, 28 Sep, 2017.)*

But in making its case to the committee, FDA did more than just explain the defects in the studies in DMD. The agency also brought up the failure of the drug in cystic fibrosis. That was, to put it mildly, an unusual approach to an advisory committee discussion. FDA, however, didn't just raise the point in passing. It came up in the introductory remarks to the committee and in the formal FDA presentation, and again in discussion/Q&A. *(Also see "Cystic Fibrosis Failure Weakens PTC's Duchenne Argument, FDA Says " - Pink Sheet, 3 Oct, 2017.)*

The *Kalydeco* precedent itself also came up – as part of PTC's argument that FDA isn't applying the same flexibility to ataluren as it has for other approvals.

When asked to respond directly to that point, FDA Team Leader Nicholas Kozauer didn't specifically cite *Kalydeco.* He did, however, describe examples of "considerations" FDA can make, including "high prior efficacy in similar or other diseases." That can establish a "high prior," that in turn serves as supportive evidence for a study in a second indication that "for some reason" fails to meet its endpoint.

PTC, unfortunately, had the opposite experience. Proven efficacy in one use can help a targeted therapy clear the bar for future indications. But, it seems, failure in one use can also help torpedo a finding of efficacy in other indications just as easily.

*From the editors of the RPM Report.*
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# Right-To-Try Legislation Must Change Language To Narrow Spectrum Of Patients, Gottlieb Says

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The Senate's right-to-try legislation should be narrowed to specify patients who are "terminally ill" as a criterion for experimental drug eligibility from its current language of "a life-threatening disease or condition," US FDA Commissioner Scott Gottlieb urges lawmakers.


Testifying before the House Energy and Commerce Subcommittee on Health Oct. 3, Gottlieb cautioned that Sen. Ron Johnson's (R-Wisc.) right-to-try legislation, known as the Trickett Wendler Right-to-Try Act (S.204), would encompass too broad a patient population. The bill in its current form could apply to patients with chronic illnesses such as diabetes or other diseases that don't immediately set a patient on a terminal course, but that are still life-threatening, the commissioner said.

"If you look across the state laws in states that have passed right-to-try laws, the language typically speaks about a patient being terminally ill to qualify for consideration under the right-to-try provisions," Gottlieb said. "Congress, in consideration of some of this legislation … has broadened that to include diseases that are either terminal or life threatening.

"The component of a life-threatening disease is a broader definition. … There are a lot of illnesses that are certainly life-threatening, but not immediately terminal."

In his prepared remarks, Gottlieb recommended defining a terminal illness as "a stage of disease in which there is a reasonable likelihood that death will occur within a matter of months."

Drugmakers could be incentivized to produce more product in the pre-approval setting through a change in clinical trial design, Gottlieb said, but he stressed that the issue is not addressed in the bill.

Johnson's right-to-try law has the goal of increasing access to investigational drugs in accordance with state right-to-try laws. The Senate passed the bill by unanimous consent the same day it voted to pass the FDA Reauthorization Act (FDARA). *(Also see "Not Quite FDARA Add-Ons: Right-To-Try, Patient Experience, Opioid Measures Also Clear US Senate" - Pink Sheet, 3 Aug, 2017.)*

The Senate, however, may not be welcome to any changes the House makes to the bill. Rep. Greg Walden (R-Ore.), who chairs the full Energy and Commerce Committee, explained that at least one Senate sponsor of the bill told him that the upper chamber is not looking for any changes "out of fear it may fail if it goes back with changes."

Gottlieb explained that the broad "life-threatening" diseases definition could force FDA to interpret the bill "expansively," and that it could "sweep in a whole range of conditions for which it didn't intend."

"The more we broaden this provision, and the more we potentially sweep in conditions for which we might be exposing people to unwanted side effects from experimental therapies, the more we risk undermining the whole venture that we are trying to engage in here, which is to narrowly tailor something to people who really don't have good options from available therapy," Gottlieb said.

In addition to the Senate legislation, Rep. Andy Biggs, R-Ariz, is sponsoring the Right to Try Act of 2017 (H.R.878). Bigg's bill uses the phrase "terminal illness" instead of "a life-threatening disease or condition." The bill defines terminal illness in accordance with state laws.

The House bill has 43 co-sponsors, which includes four Democrats. Other Democrats, however, such as subcommittee Ranking Member Gene Green (D-Texas), have raised concerns about right-to-try legislative efforts taking FDA out of the equation.

The fate of legislative efforts remains unclear. Subcommittee Chairman Rep. Michael Burgess (R-Texas) closed out the hearing noting that the conversations "set the stage for perhaps our second hearing in this regard," adding that "clearly, this is not the end of the story."

## AVAILABILITY, SAFETY ALSO ISSUES

The commissioner maintained FDA's usual stances on the issue of expanded access, noting that the agency approves 99% of requests, and that it can approve emergency requests over the phone within 24 hours.

For the requests that were denied, Gottlieb explained that roughly half have been due to the experimental drug not being available.

"The biggest reason is that when companies do clinical trials, they don't have continuous manufacturing," Gottlieb said. "They don't have large facilities online pumping out endless supplies of drugs. They will do what we call 'discontinuous batches.' They will do runs just to create batches of drug supply and active pharmaceutical ingredient sufficient for the clinical trial."

Gottlieb said that drugmakers could be incentivized to produce more product in the pre-approval setting through a change in clinical trial design, but stressed that the issue is not addressed in the bill.

In other cases, Gottlieb said, the denial comes as a result of a clinical hold, which the public doesn't know about since the hold is confidential information.

## NOT A PERFECT SYSTEM, BUT A VERY GOOD ONE

Gottlieb noted at the hearing that FDA's expanded access system over the years has not been perfect, it has been remained effective.

In an Oct. 3 FDA Voice blog post, the commissioner touted several measures that the agency has taken to remove hurdles that delay or discourage expanded access applications. He announced that physicians now only need approval from one Institutional Review Board (IRB) member – either the chair or another "appropriate" member – at their facility to treat a patient under expanded access. Previously, physicians were required to obtain approval from the full board.

IRB requirements were clarified in both the "Form FDA 3926" guidance, as well as the "Waiver of IRB Requirements for Drug and Biological Product Studies" guidance.

"This is an important step to protect the rights, safety and well-being of human subjects in clinical research – but assembling the full board may cause delays because they may not routinely meet," Gottlieb writes.

"I believe the simplified IRB process will facilitate access while still protecting patients."

He also announced in the blog post that FDA has its June 2016 Q&A guidance with clarifications about how sponsors should adverse event data for expanded access investigational new drug applications (INDs). The updated guidance specifies that sponsors are only required to report adverse events "if there is evidence to suggest a causal relationship between the drug and the adverse event."

Sponsors have often been hesitant to provide drugs under the expanded access program with the uncertainty about how FDA will view the product's adverse event data in the review process.

Gottlieb worked to assuage these fears at the hearing, however, pointing to a Government Accountability Office (GAO) report that found that have only been two instances where adverse events from expanded access use contributed to a decision to put development of an investigational drug on a partial clinical hold. *(Also see "Expanded Access: FDA To Clarify How Adverse Events Impact Drug Approval Process" - Pink Sheet, 20 Jul, 2017.)*

The commissioner added in his blog post that more "simplifications and clarifications" regarding the expanded access program are on the way.

### INDUSTRY REP NOT A FAN

An industry representative at the hearing, **Cognition Therapeutics Inc.** President and CEO Kenneth Moch, was the harshest critic of the right-to-try legislation at the hearing.

Along with Gottlieb, Moch explained that the legislation cannot force drugmakers to provide their experimental products to patients. Moch added that FDA has never been a hindrance to granting expanded access requests, and that the legislation also does not take into the account the complexities of drug development.

"No ethical company that I know of would ever release an experimental medicine outside of the FDA's regulatory process. A basic mantra is that 'all drugs have side effects.' And cutting scientific corners creates unbounded risks."

Moch further criticized anecdotal arguments in favor of right-to-try legislation, and stressed that taking FDA out of the equation does nothing to address the reasons as to why drugmakers don't provide access to experimental treatments.

"You have to look at the totality [of data]," Moch said, also referring to the bill as "feel-good legislation."

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# Crack-Down On Homeopathic Products Pushed By EU Science Advisory Council

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European regulatory bodies should establish a "standardized, knowledge-based" regulatory framework for homeopathic products, which too often bear "implausible" scientific claims and present a risk to consumers under the current lax approach, says an umbrella organization of 29 European scientific bodies.

The framework should cover product efficacy, safety and quality and advertising practices across the EU, similar to the standards that exist for other types of drug products, the European Academies Science Advisory Council (EASAC) recommends in a recent 12-page statement intended to "reinforce" recent criticism of the alternative medicines by member academies from all over the EU. These include the Royal Society in the UK, the Royal Swedish Academy of Sciences, the Royal Danish Academy of Sciences and Letters and the German National Academy of Sciences Leopoldina.

Homeopathic medicine is rooted in the idea that a substance that causes symptoms of a disease in a healthy person can cure similar symptoms in a sick person. Formulas often are manufactured using a process of homeopathic dilution, in which a substance


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“Claims supporting the alternative medicine products often are “inconsistent” with established scientific concepts and “there are no known diseases for which there is robust, reproducible evidence that homeopathy is effective beyond the placebo effect.”

is repeatedly diluted in alcohol or distilled water to the point where often no molecule of the original substance remains but the substance is said to be “imprinted” in the formula, EASAC notes.

Homeopathic products account for 7% of the total EU market for nonprescription medical products, according to EASAC. Growing at a rate of 6% annually, homeopathic products reached a value of more than €1bn ($1.17bn) in the EU in 2015, the council notes.

Claims supporting the alternative medicine products often are “inconsistent” with established scientific concepts and “there are no known diseases for which there is robust, reproducible evidence that homeopathy is effective beyond the placebo effect,” it states.

The umbrella organization believes products without solid science should not be approved or registered by national regulatory agencies for the designation as a medicinal product. Further, EASAC says evidence-based, public health systems should not reimburse homeopathic products and practices unless they are demonstrated to be efficacious and safe by rigorous testing standards that apply to other categories.

“There must be parity of assessment in medicine,” the council asserts.

## CURRENT APPROACH BASES SAFETY ON DILUTION

In the EU, homeopathic products are regulated under a directive that requires member states to ensure formulas can be registered without proof of therapeutic efficacy, provided there is a significant degree of dilution from the original stock to guarantee safety of the product (at least 1 in 10,000). Other medicinal products must fulfil legal requirements for terms of quality, safety and efficacy, and must meet principles of good manufacturing, distribution and pharmacovigilance practices.

Further, unlike other product categories, homeopathic products are exempt from EU labeling regulations requiring listing all ingredients and quantities. Instead, labels must contain the scientific name of the stock material, followed by degree of dilution.

In response to the EU directive, Member States have introduced various regulatory schemes. However, there are two general procedures by which most states allow homeopathic products to be registered:

- Simplified registration scheme – Manufacturers must submit data on the quality of the product and show it is diluted enough to guarantee safety, however, the scheme does not allow for indications.
- National rules scheme – Manufacturers submit data on quality and safety to allow a claim for specific conditions (minor symptoms and conditions, which do not require the supervision of a doctor).

## SAFETY, EFFICACY QUESTIONED ACROSS EU

Scientific academies and doctors’ groups have been sounding the alarm against homeopathic products in recent years. In 2015, the Standing Committee of European Doctors expressed concern that the mostly unregulated status of the products in many EU member states may pose significant risks to patient health and safety.

## EASAC RECOMMENDS:

- “There should be a consistent regulatory requirement for claims for the efficacy, safety and quality of all medicinal products to be based on verifiable and objective evidence, commensurate with the claims being made. The necessity for robust data applies to products for both human and veterinary medicine. In the absence of robust and verifiable evidence, a product should not be approvable by national regulatory agencies for the designation medicinal product.”
- “Public health system budgets are under increasing pressure. Evidence-based public health systems should not offer reimbursement for homeopathic products and services unless they are demonstrated to be efficacious and safe by rigorous testing.”
- “The composition of homeopathic products should be labelled in a similar way to other health products available in the pharmacy (OTC) or elsewhere. That is, the current exceptional labeling permitted for homeopathic products should be replaced by a simple description of the ingredients and their amounts present in the formulation.”
- “Advertising and marketing of homeopathic products and services must be regulated to be accurate and clear: advertising claims made for efficacy and safety should not be allowed without demonstrable and reproducible evidence.”

The same year, the Royal Swedish Academy in 2015 released a statement critical of a report from the Swedish Medical Products Agency discussing incorporation of homeopathic products into the country's directive on medicinal products. The academy said there is no scientific evidence for clinical effects of the products and high dilution rules out effects by any known mechanisms.

In the UK, the homeopathic category is on the chopping block of England's National Health Service, which in August released a proposed list of "ineffective and dangerous" medicines that are cut from its budget. In addition to homeopathics, the agency identified traditional herbs and medicines and certain prescribed products, including fentanyl, an opioid pain medication, and erectile dysfunction drug tadalafil, that it says should no longer be prescribed by primary doctors in England. *(Also see "NHS England Tackles Use Of 'Ineffective And Dangerous' Medicines" - Pink Sheet, 14 Aug, 2017.)*

NHS placed the identified categories in a draft national guidance for Clinical Commissioning Groups on drugs that can be considered as low priority for NHS funding. Following a stakeholder meeting in June, the draft was published for comment for a three-month consultation period that closes Oct. 21.

## RECS FOR EMA

EASAC says it is not pushing for the prohibition of homeopathic products. "We recognize the fundamental importance of allowing and supporting consumer choice. Rather, we aim to explore policy dimensions for ensuring informed patient choice with the emphasis on 'appropriately informed' and for achieving a standardized knowledge-based, robust regulatory framework and sound advertising practices across the EU."

The council made recommendations for policy makers in EU institutions and in Member States, to its academy members, the scientific and medical communities. The recommendations should have implications for the European Medicines Agency, EASAC says.

In the US, homeopathic products are facing similar scrutiny.

In late 2016, the Federal Trade Commission published its Enforcement Policy Statement on Marketing Claims for OTC Homeopathic Drugs, stating it will hold efficacy and safety claims for the products – both in advertising and on labeling – to the same standard as other products making similar claims; marketers must support health claims with competent and reliable scientific evidence.

The policy statement also advises that the agency expects firms to add disclaimers, including lengthy statements where needed, to products labeled with a treatment indication. *(Also see "OTC Homeopathic Labels Must Include Scientific Disclaimers – FTC" - Pink Sheet, 15 Nov, 2016.)*

The US market for homeopathic products was valued at more than $3bn in 2015, notes EASAC.

*From the editors of The Tan Sheet.*
*Published online October 3, 2017*

# Turkey Poised To Stretch Consumer Health Market; Rigid On Ads, Access

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Between 10% and 15% of Turkey's Rx drugs will become available OTC under a proposed regulation by the country's health care regulator that would expand its consumer health product market from around 80 products to more than 1,000.

The Ministry of Health and the Turkish Medicines and Medical Devices Agency, however, don't appear ready to alter the country's prohibition on advertising for pharmaceutical products and allow ads for OTCs, nor to allow sales of the products outside of pharmacies.

Although some 80 pharmaceutical and vitamin products already are available nonprescription in parts of Turkey, the proposal, in development for almost two years by the ministry and TMMDA, would be the country's first regulation for sales of consumer health care products.

The proposal includes OTC drug categories of cough/cold, allergy, analgesic and antipyretic, dermatology and gastrointestinal in addition to vitamins, minerals and dietary supplements.

According to Turkish market data from IMS, spending on products in those categories currently available by prescription was around $1.73bn for the year ending May 2016. The top categories are vitamin, cough/cold, allergy and analgesic products, though sales in each category has been somewhat flat since 2012 *(see charts)*.

## ADS NOT NOW, MAYBE LATER

Pharma manufacturers have lobbied the ministry and TMMDA to allow advertisements for brand OTC products, but pharmacists and medical professional associations remain opposed, arguing that ads would be misleading for patients who don't have knowledge to make a safe decision.

TMMDA officials agree with health care providers. Agency President Hakki Gursoz has emphasized multiple times that pharmacists will be patients' primary advisors on OTC drugs.

While advertisement in national publications, TV or online will not be allowed, pharma firms still hope for some ad room on publications targeting industrial and


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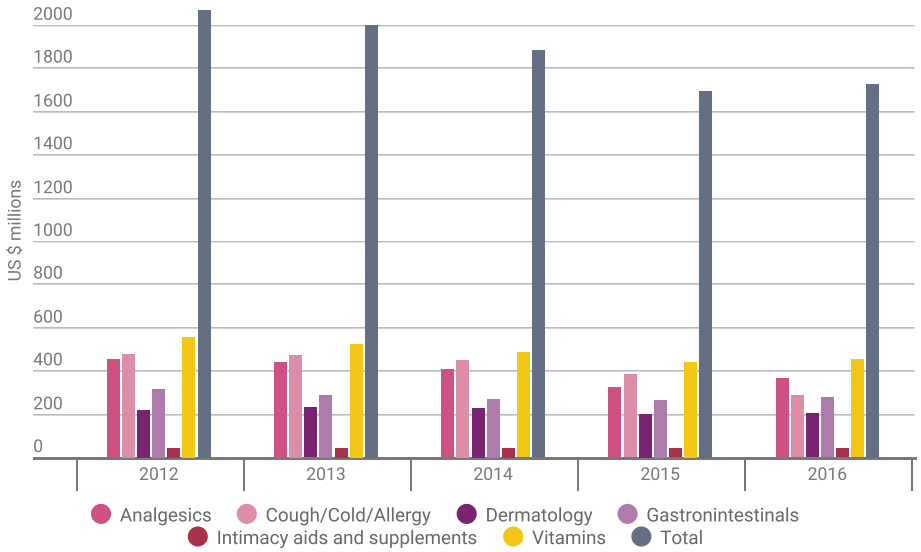
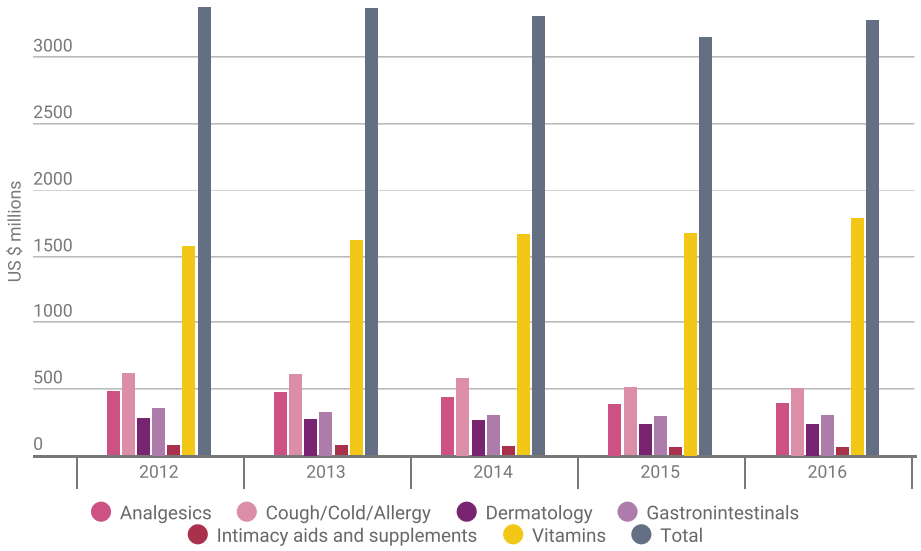
## Sales* In Turkey's Potential OTC Categories

### Reimbursements




### Total Spending




Products in these categories currently available Rx-only Turkey would become available OTC in pharmacies under a proposed regulation. (* US$ millions)

*Source: IMS data*

professional sectors. Moreover, pharmacist and doctor groups expect ads in consumer publications and TV eventually will allowed because of the additional advertising revenues that would result.

### PRICING POLICY NOT SO CLEAR

Less has been said so far about the proposed regulation's oversight of pricing. Currently, Turkey reimburses consumers for all Rx drugs, including those likely to be made nonprescription. *(Also see "Will Turkey Ever Regulate Its OTC Market?" - Pink Sheet, 10 Aug, 2016.)*

One goal of adding an OTC market regulation is reducing the financial burden on the country's Social Security Institution.

And pharma firms that market brands in Turkey want the country to take remove some OTC products from the reimbursement list and allow them to determine the prices based on consumers' uptake. The Association of Research-based Pharmaceutical Companies research group made this argument at any opportunity it has in meetings with ministry and TMMDA officials.

However, government officials and industry stakeholders also know many consumers would prefer being reimbursed for Rx drugs than paying out of pocket for an OTC product that would provide the same treatment. While eliminating some OTCs from eligibility for reimbursement would allow pharma marketers potentially to raise prices they charge in the country, the change also likely would increase Turkey's overall reimbursement spending.

### PHARMACIES KEEP THEIR MARKET

A second industry group interested in the regulation, chain retailers, has not had as much influence on the ministry's decisions. Although businesses already operating retail chains and others looking to enter the space argued to allow sales of OTC drugs in venues other than pharmacies, the ministry and TMMDA remain committed to limiting all drug sales to pharmacies.

As sales by retail chains percolated as a topic in discussions on Turkey's developing OTC drug regulation, pharmacists grew leery of losing expected growth in their consumer health product sales to new competitors that also sell myriad consumer products not available in pharmacies.

However, their own lobbying apparently is paying off. As pharmacists are well organized and exert influence through their associations, they also emphasized that OTC drugs and vitamins should be sold through pharmacies, even though expanding the retail channels would have increased their overall sales.

Turkey officials had planned to publish a regulation earlier in 2017, but forging agreements on details of the rule has prolonged the process and the ministry has not updated its expectation for completing the work.

*From the editors of PharmAsia News.*
*Published online September 29, 2017*

# Recent And Upcoming FDA Advisory Committee Meetings

| TOPIC | ADVISORY COMMITTEE | DATE |
|---|---|---|
| Selection of strains to be included in an influenza virus vaccine for the 2018 southern hemisphere influenza season | Vaccines and Related Biological Products | Oct. 4 |
| Spark Therapeutics' *Luxturna* (voretigene neparvovec) for treatment of vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy | Cellular, Tissue, and Gene Therapies | Oct. 12 |
| Aerie Pharmaceuticals' netarsudil ophthalmic solution 0.02% for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension | Dermatologic and Ophthalmic Drugs | Oct. 13 |
| Novo Nordisk's semaglutide injection as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus | Endocrinologic and Metabolic Drugs | Oct. 18 |
| Indivior Pharmaceuticals' buprenorphine subcutaneous injection for treatment of opioid dependence | Psychopharmacologic Drugs/Drug Safety and Risk Management | Oct. 31 |
| Braeburn Pharmaceuticals' buprenorphine subcutaneous injection for treatment of opioid dependence | Psychopharmacologic Drugs/Drug Safety and Risk Management | Nov. 1 |
| Clinical development plan for Pfizer's Staphylococcus aureus vaccine intended for pre-surgical prophylaxis in elective orthopedic surgical populations | Vaccines and Related Biological Products | Nov. 7 |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