Pink Sheet
pink.pharmaintelligence.informa.com Vol. 79 / No. 49 December 4, 2017
Pharma intelligence informa

Medicare Price Negotiations: HHS Nominee Suggests Adapting Part D 'Learnings' To Part B

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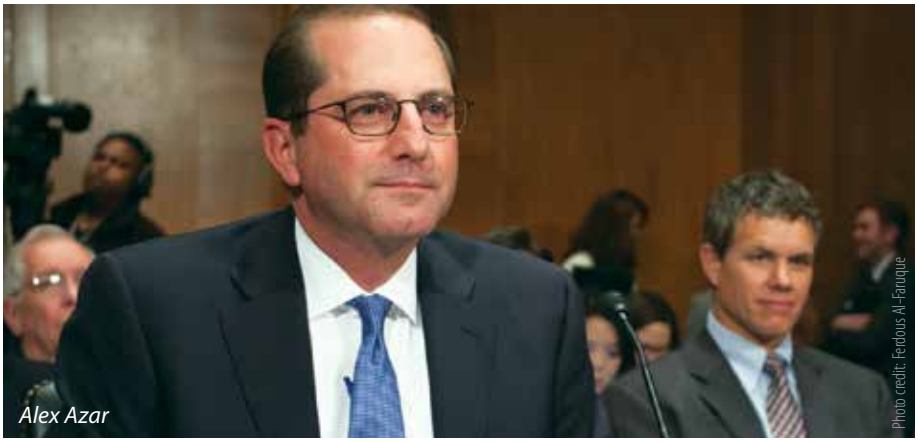
Alex Azar

Photo credit: Ferdous Al-Faruque

HHS Secretary nominee Alex Azar is interested in exploring some form of price negotiations in Medicare Part B to help lower costs for the government and beneficiaries, he told the Senate Health, Education, Labor and Pensions Committee at a courtesy confirmation hearing Nov. 28.

The hearing served as a forum for members on both sides of the aisle to ask about Azar's views on drug pricing in light of his previous tenure as a senior executive at **Eli Lilly & Co.** In his testimony, he identified lowering drug prices as one of the highest priorities for his "personal efforts" as head of HHS. He also talked about finding ways to stop manufacturers from "evergreening" patents as a price-lowering measure. *(Also see "Azar's HHS: Generic Certainty, REMS Fixes Can Lower Drug Prices" - Pink Sheet, 29 Nov, 2017.)*

Azar's appointment was announced Nov. 13. *(Also see "HHS Nominee Azar: Great News For Industry But ACA Reform Will Be Priority" - Pink Sheet, 13 Nov, 2017.)* The Senate Finance Committee will also hold a confirmation hearing for Azar and that session will include a vote on the nomination ahead of consideration by the full Senate. A date for the Finance Committee hearing has not been announced.

Azar's comments regarding Medicare came in response to a question from Sen. Al Franken, D-Minn., who asked whether he agreed with past statements by President Trump on bringing direct government price negotiations to Medicare Part D to help lower costs.

"The president has generally spoken about the desire to ensure that Medicare is negotiating and getting the best deal possible with drugs," Azar said. "Part D actually has negotiation through the three or four biggest pharmacy benefit managers. They negotiate and actually secure the best net pricing of any players in the commercial system – I sat on the other side of that and I can assure you of this."

However, he continued, "what I'd like to do is think about how we can take the learnings in Part D maybe into Part B. Part B does not have negotiation. … The government simply pays the sales price plus six percent. So how could we think about ways to take the learnings from Part D and actually bring lower costs to the system but also lower costs to the patient, because they pay a share of whatever Medicare reimburses in Part B." That could be a "double win."

Azar did not go into detail about his ideas but industry should be reassured that 1) he is not advocating direct HHS negotiations in Part D and 2) he appears to be envisioning a market-based process for negotiation in Part B.

Azar also mentioned negotiations in Part B at the BIO CEO & Investor conference in February and those comments may shed some light on his thinking.

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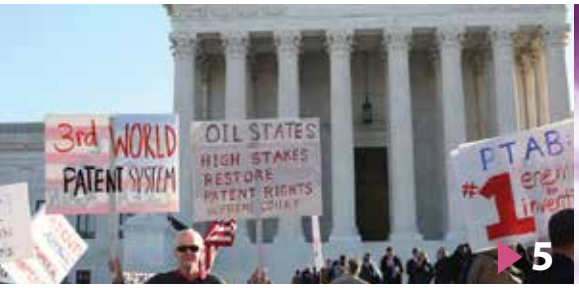

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French Competition Probe Targets Price Setting, Distribution, And Generic Rebates

https://pink.pharmaintelligence.informa.com/PS122054

Four years after its last inquiry into competition in the pharmaceutical market, the French competition authority is to look into how the prices of medicines are set, the level of rebates in the generics market, and the "economic and competitive balance of the pharmaceutical distribution chain."

FDA's Nicotine Replacement Standards Review Could Open Door For E-Cigarettes

https://pink.pharmaintelligence.informa.com/PS122051

Latest steps by US FDA targeting tobacco-related health problems are a Nicotine Steering Committee, headed by Commissioner Gottlieb, and a public docket, including a meeting in January, for suggestions on how novel products could be evaluated as safe and effective NRTs.

India Sets Out Modalities Of Perpetual Licensing Initiative

https://pink.pharmaintelligence.informa.com/PS122047

India has outlined key aspects of its recently introduced perpetual licensing system, including initial modalities around joint inspections of manufacturing units by central and state drug inspectors.

Azar's HHS: Generic Certainty, REMS Fixes Can Lower Drug Prices

https://pink.pharmaintelligence.informa.com/PS122049

During Senate Health, Education, Labor and Pensions Committee hearing on the former Eli Lilly executive's nomination for HHS Secretary, Alex Azar said department should consider whether REMS still necessary upon generic entry.

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(Also see "Sweeping FDA Changes Could Have "Disastrous Consequences" For Biotech Investment" - Scrip, 15 Feb, 2017.)

"When the president says something, eventually the government will do something," he said. "In the policy world, we hear 'negotiate drug price,' and we go right to a certain place" – negotiations in Part D. But "that may not be what the president means when he uses those words."

He suggested "there are some interesting things in Part B" that could be done. "Maybe you try some competitive acquisition programs, commission PBMs to make competitive acquisition negotiations of Part B drug pricing as an alternative to" the average sales price plus 6% reimbursement formula currently in place.

Azar framed his previous experience at HHS as deputy director during the implementation of Part D and his later experience in the industry as important assets for addressing drug pricing.

"Through my experience helping to implement Part D and with my extensive knowledge of how insurance, manufacturers, pharmacy, and government programs work together, I believe I bring skills and experience to the table that can help us address these issues, while still encouraging discovery so Americans have access to high quality care."

But Democrats on the HELP committee were skeptical. In response to a question from ranking member Patty Murray, D-Wash., on whether his industry ties might influence his decisions, he said: "If I am confirmed, I do hope I can earn your trust and will show you that this is the job of a lifetime for me, and I would approach this not for any industry, not for any past affiliation, but to serve all Americans, to improve their health and well being."

INSULIN PRICE HIKES WHILE AT LILLY

In the opening question at the hearing, committee Chairman Lamar Alexander, R-Tenn., asked Azar to address why the price of Lilly's insulin products increased significantly during the time he led the US company as president, noting that has been the source of concern for some members. The issue was later brought up by a number of Democrats and by Sen. Rand Paul, R-Ky.

> "This is the job of a lifetime for me and I would approach this not for any industry, not for any past affiliation, but to serve all Americans, to improve their health and well being."

In response, Azar mostly blamed the system but also stated that things should change to protect patients.

"The price of many drugs has risen substantially, and in particular insulins, he said. "The current system for pricing insulins and other medicines may meet the needs of many stakeholders but that system is not working for patients who have to pay out-of-pocket and we have to recognize that impact. That's why the president, so many members of this committee on a bipartisan basis and I have talked about the need to fix this system."

He added, "I do think my experiences [help me] in … understanding how the channel works, how the channel sees these issues, how manufacturers, pharmacy benefit managers, pharmacies and distributors all work together, how the money flows. In that I believe I can hit the ground running to work with you and others to identify solutions."

Sen. Tammy Baldwin, D-Wisc., noted that at the committee's mid-October hearing on drug pricing, stakeholders involved in the supply chain accused each other of responsibility for high drug prices and failed to express consensus on a remedy. *(Also see "Drug Pricing Legislation Appears Nowhere In Sight Following Senate Hearing" - Pink Sheet, 17 Oct, 2017.)*

"Finger pointing is not constrictive," Azar agreed. "Everybody owns a piece of this. … I think the government owns a piece of this. And that's why I want to serve." The system "has got to get fixed, that's the problem."

NO SUPPORT FOR IMPORTATION

Azar withheld support for the idea of importation as a solution to drug prices. In an exchange with Paul, who pointed out that President Trump advocated importation, Azar said: "I have before publicly stated a position against unsafe importation of drugs into the United States. The president has said the same." He also pointed out a "succession of FDA commissioners have said they would be unable to certify" the safety of imported drugs under current law.

Paul said the commissioners "have been wrong and beholden to the drug companies and that the notion that importation from Europe, Canada and other developed countries is unsafe "is a canard." He added the committee will ask Azar for more justification about his concern that drugs imported from the European Union, for example, are not safe and to discuss how to make them safe.

"Convince me you at least are open to it and will not just say it's unsafe," Paul said. "If you can't do that, I can't support you. So I hope you come back with an answer."

In his closing comments, Alexander outlined some drug pricing policy issues the committee is interested in exploring, with Azar's input. The HELP panel is planning another drug pricing hearing Dec. 12 to address an upcoming National Academy of Sciences, Engineering and Medicines report on making drugs affordable.

"Drug pricing is complicated … byzantine," Alexander told Azar. "You arrive knowing the subject and helping us answer the questions, Where does the money go? Do we really need rebates? Can there be more negotiations on drug pricing? Should we really think seriously about finding a way to let Americans buy drugs that are not approved by the FDA? We have never done that before and several senators think we should. And we should talk about that."

Published online November 29, 2017

Supreme Court Seems Likely To Keep Inter Partes Review Despite Problems

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US Supreme Court justices seemed divided on whether the US Patent and Trademark Office's inter partes review (IPR) patent challenge proceeding violates the Constitution by allowing an administrative proceeding to decide the validity of patents in place of district courts.

The justices heard oral arguments Nov. 27 in Oil States Energy Services LLC v. Greene's Energy Group LLC. The question before the court is whether the IPR process is unconstitutional because it eliminates the right to a jury trial. Petitioners contend that cases to invalidate patents must be tried before a jury in an Article III forum (the courts established under Article III of the Constitution), not adjudicated in an administrative agency proceeding.

"I think it will be a split decision," Naveen Modi, a partner at Paul Hastings, said in an interview following the arguments.

Modi noted that a few justices, including Ruth Bader Ginsburg, Elena Kagan, and Sonia Sotomayor, indicated that they were probably okay with the inter partes review proceeding as long as it is subject to judicial review by the US Court of Appeals for the Federal Circuit. But others seemed bothered by instances of panel stacking – in which the PTO assigns Patent Trial and Appeal Board (PTAB) panel members to reach a decision that is in line with patent office policies. Neil Gorsuch seemed inclined to rule against the proceeding.

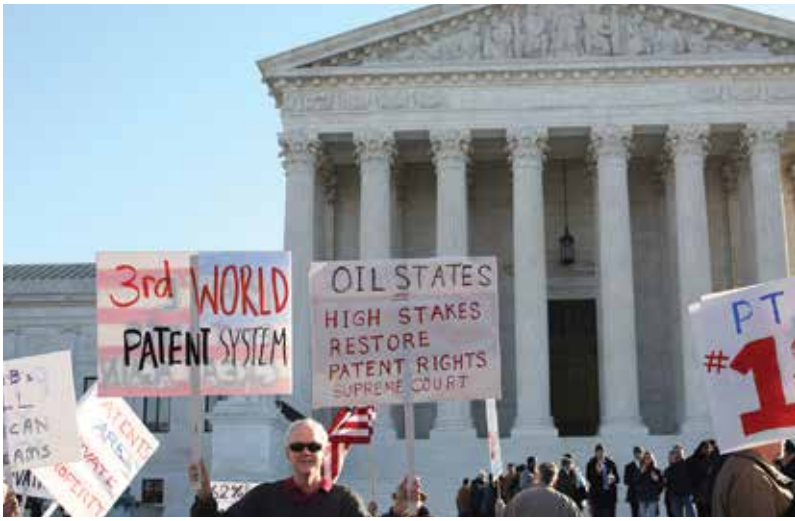

Photo credit: Brenda Sandburg

INDEPENDENT INVENTORS PROTEST

The case is critical to the biopharmaceutical industry which sees IPR as a major threat to their intellectual property as it can lead to repeated challenges to the same patent and result in opposing rulings by the district court and PTAB. Generic manufacturers argue that it allows generic and biosimilar sponsors to get the patent office to take a second look at patents and weed out those that were granted in error.

The Biotechnology Innovation Organization and Pharmaceutical Research & Manufacturers of America each filed briefs arguing that the proceeding is unconstitutional, as did **AbbVie Inc.**, **Allergan PLC**, **Celgene Corp.**, and **Shire PLC**. The Association for Accessible Medicines and Mylan filed briefs advocating for IPR, as did numerous companies in the tech industry. *(Also see "Will Inter Partes Review Go Away? Supreme Court Weighs Fate" - Pink Sheet, 17 Nov, 2017.)*

The entire patent community has been riveted by the case and the courtroom was packed. There was also a demonstration outside by independent inventors organized by the group US Inventor. They contend that PTAB has invalidated patent claims at an alarming rate and suffers from due process issues. Asked about his opposition to IPR, protester Alan Beckley, from Plano, Texas, cited the experience of Josh Malone, who invented Bunch o Balloons, which enables 100 water balloons to be filled quickly. TeleBrands filed a petition with PTAB challenging Malone's patent and the board found it invalid.

WHEN CAN PATENT OFFICE CORRECT ERROR?

Justice Ginsburg posed the first question, asking if there must be some way for the patent office to correct errors made with respect to missing prior art. "Do you recognize any error correction mechanism as within Article III?" she asked.

Oil States attorney Allyson Ho, a partner at Morgan Lewis, responded that the PTO is not precluded from correcting errors, but simply can't do it through IPR adjudication. She made a distinction between the PTO's reexamination proceedings, which are fundamentally proceedings between the patent office and the patent owner, and inter partes review.

Congress authorized ex parte reexaminations before the PTO in 1980 and inter partes reexaminations in 1999. The IPR replaced the inter partes reexamination proceeding, which also allows a third party to petition the PTO to reexamine the patentability of an issued patent and to participate in the proceeding. Ex partes reexams, which are still in effect, do not permit third party participation in reviews.

Justice Kagan asked where Ho would draw the line between ex parte and inter partes reexamination and IPR. "So, what's the line? What are the procedures that are here that you think make this essentially adjudicatory that are not in those other proceedings?" she asked. Is it discovery or the ability of the petitioner to participate in the hearing?

Chief Justice John Roberts Jr. asked why, if the government can restrict property rights it cannot do the same with patent rights. Ho responded that Congress is taking a category of cases that have

been adjudicated in courts for centuries and moving them to a non-Article III tribunal.

Ginsburg jumped in saying that the move is for "a very limited purpose" of determining the existence of prior art, i.e., existing inventions.

'BITTER WITH THE SWEET'

Justice Gorsuch seemed the most sympathetic to Oil States' position. He noted that the Supreme Court has arguably addressed the issue in other cases, saying only courts have the authority to set a patent aside or to correct it for any reason. He asked Ho why she did not stake her ground and just say anytime a private right is taken by anyone, it has to be through an Article III forum.

The patent community has speculated that the Supreme Court took up the case only after Gorsuch was appointed to the court. It had denied cert petitions for three other IPR cases raising the same question of the proceeding's constitutionality.

Justice Stephen Breyer said he thought it is "the most common thing in the world that agencies decide all kinds of matters through adjudicatory-type procedures often involving private parties." But in questioning Greene's Energy Group's attorney Christopher Kise, a partner at Foley & Lardner, he expressed concern about someone requesting reexamination of a patent that has been in existence for 10 years and for which a company has invested $40bn.

"Do people gain a kind of vested interest or right after enough time goes by and they rely on it sufficiently so that it now becomes what?" he asked. "Is there something in the Constitution that protects a person after a long period of time and much reliance from a reexamination at a time where much of the evidence will have disappeared?"

Kise replied, no. And Justice Kagan then asked what about if there were no judicial review at all. "Then you would have to say yes, right?"

Kise said he did not know if he would have to say yes since the patentability determination is being made by the executive branch and adjudications are not themselves inherently judicial.

Justice Roberts responded that Kise's position "is simply that you've got to take the bitter with the sweet. If you want the sweet of having a patent, you've got to take the bitter that the government might reevaluate it at some subsequent point." But he said that the court has rejected this proposition. For example, in the case of public employment, he stated, someone can't be terminated in a way that's inconsistent with due process.

PANEL STACKING

Regarding due process, Roberts said that if the PTO director doesn't agree with the direction that PTAB panels are going, she can add new judges to the panel so it is a tool of executive activity rather than anything resembling determination of rights.

Kise replied that he did not believe the panel packing had occurred more than one or two times. Deputy Solicitor General Malcolm Stewart, who argued on behalf of the government, said that changes to the panel during the proceeding had occurred three times when the chief judge of PTAB "was concerned that the panel as initially composed was likely to diverge from general PTAB precedent with respect to a matter that bore on the institution decision, and so the chief judge expanded the panel."

Stewart added that it's not clear whether the chief judge picked judges that he had reason to think would be sympathetic to a particular view.

Justice Anthony Kennedy asked what would happen if the panel stacking were rampant, to which Kise replied that the Administrative Procedures Act and other provisions of the Constitution would deal with any shenanigans.

Justice Sotomayor replied, this is "what troubled me deeply" and what saves this [the IPR decision] is that it can be appealed to a court.

"So how can you argue that the crown, the executive, the PTO here has unfettered discretion to take away that which it's granted?" she asked.

Justice Gorsuch added that there is only judicial review if somebody appeals the PTAB decision.

INVESTMENT QUESTION

Justice Breyer returned to his concern about having someone's patent challenged after billions of dollars have been invested in it. Addressing Deputy Solicitor General Stewart, he said, "what I'm thinking, quite seriously, is saying should we leave open, assuming I basically agree with you, but leave open the question of what happens if there has been huge investment?"

Stewart replied that in theory you could reserve it but that to suggest that invalidation of a patent was potentially vulnerable on that basis would cause many more problems than it would solve.

COURT RULING EXCEPTIONS?

The IPR proceeding was established under the America Invents Act of 2011 as a cheaper, faster alternative to district court litigation. It is considered more favorable to patent challengers as it does not presume patent validity, has a lower burden of proof ("preponderance of the evidence" versus "clear and convincing" evidence), and uses the "broadest reasonable interpretation" standard for determining the meaning of patent claim terms, which allows the consideration of more prior art and increases the chances that a patent will be held invalid.

The Supreme Court unanimously upheld the PTAB's use of the broadest reasonable interpretation standard last year in Cuozzo Speed Technologies LLC v. Lee. In that case the court also ruled 6-2 that PTAB decisions to institute review are not appealable. Justices Samuel Alito and Sotomayor dissented. *(Also see "Supreme Court Upholds IPR Standard Making Patent Invalidation Easier; Will Congress Reverse?" - Pink Sheet, 20 Jun, 2016.)*

As for how the justices may rule in this case, Modi said the court could say IPR is constitutional and leave other issues about the proceeding to address another day. If they find it is unconstitutional, he believes Congress will step in quickly and try to fix it.

Paul Hastings partner Igor Timofeyev said the court may uphold the IPR process but not want to write Congress a blank check. Justices were bothered by patent misuse, such as panel stacking, and you may see them make exceptions where the decision doesn't apply, he said.

Published online November 28, 2017

UK Industrial Strategy Offers 'Substantial' Life Science Investments Through New Sector Deal

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A key element in the UK Industrial Strategy white paper announced by the government on Nov. 27 is what the government describes as a "multi-billion pound" sector deal for the life sciences to ensure the UK produces "new pioneering treatments and medical technologies" to improve patients' lives and drive economic growth.

The sector deal, which is expected to be signed in the coming weeks, will involve "substantial" investments from both the private and charitable sectors, as well as "significant commitments" in R&D from the government.

The Industrial Strategy, which was revealed at the same time as the government announced two major R&D investments by life science firms, MSD and Qiagen, is intended to help allay growing concern over the impact of Brexit expressed across many industry sectors, particularly if no trade deal is negotiated with the EU by the end of March 2019.

It also follows the announcement by the Office for Budget Responsibility last week that it was downgrading its growth forecasts for the UK to an average of 1.4% a year over the next five years.

Business Secretary Greg Clark said the UK had a "thriving research and science base" and was home to "a wide range of innovative sectors, from advanced manufacturing and life sciences, to fintech and creative industries. The Industrial Strategy is an unashamedly ambitious vision for the future of our country, laying out how we tackle our productivity challenge, earn our way in the future, and improve living standards across the country."

LIFE SCIENCES

In the life sciences area, industry fears there will be adverse effects of Brexit on investment decisions, the free movement of medicines and researchers, regulatory alignment between the UK and the EU, and the possibility of the UK being left behind on new drug launches and multinational clinical trials.

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> "The Industrial Strategy is an unashamedly ambitious vision for the future of our country." – Business Secretary Greg Clark

The sector deal, one of four announced by the government, is expected to be based on the Life Sciences Industrial Strategy that was spearheaded by Professor Sir John Bell and revealed on Aug. 30. This industry-led project has a number of objectives, such as modernizing the way clinical trials are run, encouraging industry to invest in R&D "for the next generation of innovative products," and making more use of data and digital technologies. *(Also see "UK Life Science Strategy Urges Adoption Of Accelerated Access Review, As Govt Prepares Response" - Pink Sheet, 7 Sep, 2017.)*

Included in the sector deal, the government said, will be the Health Advanced Research Programme (HARP), which the government describes as "an ambitious shared endeavour, with the aim of finding solutions to the major healthcare challenges of the next 20 years while also creating new UK industries." It will also have ideas on expanding life science manufacturing which, "as a major source of exports, makes a significant contribution to the UK economy."

New regional Digital Innovation Hubs will support the use of data for research purposes and" create controlled environments for real-world clinical studies, the application of novel clinical trial methodology, and the comprehensive evaluation of new innovations so that patients can benefit from scientific breakthroughs much faster."

This project will be led by NHS England, NHS Digital and Health Data Research UK, with input from the life science industry, the academic and charity sectors, and patients.

INDUSTRY REACTIONS

The Association of the British Pharmaceutical Industry said the Industrial Strategy was "important in providing a long-term strategic roadmap for UK business" and that as the UK prepared to leave the EU, it was vital to keep the domestic landscape as attractive as possible.

"We now look forward to further detail on the sector deals between the pharmaceutical industry and government on the back of Sir John Bell's impressive Life Sciences Industrial Strategy," said Mike Thompson, the association's chief executive. "These deals are just the first steps but will be instrumental in securing the future strength of the UK life sciences industry, helping the UK economy prosper and allowing NHS patients to get better and faster access to world-class medicines discovered and developed here in Britain."

Similar praise came from the generics segment. Warwick Smith, director general of the British Generic Manufacturers Association and the British Biosimilars Association, said: "We welcome the government's Industrial Strategy white paper and in particular a commitment to build on the core principles

of competition, free trade and high regulatory standards, all of which are critical elements of the business environment for the UK generic medicines industry and pharmaceutical sector more widely."

As for the life sciences sector deal, he said he was "pleased to see the government restate its commitment for the NHS and industry to collaborate closely, alongside the commitment to grow life sciences manufacturing."

On the Brexit front, Smith said that like much of the pharmaceutical industry, "we have repeatedly called for a transition period of [at] least two years and so encourage efforts in this respect." The generics industry wants the UK to remain a part of the European regulatory framework – or for there to be effective systems of mutual recognition – to "ensure that no obstacles are put in the way which obstruct the efficient supply of medicines into or out of the UK in the interests of ensuring patient access to medicines," he added.

CHALLENGE FUND INVESTMENTS

As well as the four sector deals – the other three concern artificial intelligence, the automotive sector and construction – the white paper provides for a three-year, £725m investment under the Industrial Strategy Challenge Fund (ISCF) to "capture the value of innovation" and "respond to some of the greatest global challenges and the opportunities faced by the UK."

The investment includes "up to £210 million to improve early diagnosis of illnesses and develop precision medicine for patients across the UK."

"There are fatal diseases that take years to develop before they present symptoms," the strategy says. "Developing effective treatments – such as for pancreatic cancer which develops on average 14 years before symptoms present - becomes progressively harder. The challenge is to combine the wealth of data created by UK researchers with real world evidence from our health service. That will allow industry to create new products and services that will diagnose diseases earlier and help clinicians choose the best treatment for individual patients. This will save lives and set the UK at the forefront of a growing global market in diagnostics."

> "People don't make investments of this scale if they don't have the confidence that we really are building a very attractive base"
> – Greg Clark

The strategy also addresses four "grand challenges" to "put the UK at the forefront of the industries of the future". One of these is artificial intelligence, which the strategy says could help in diagnosing medical conditions more effectively.

And it mentions last week's announcement by the government that it aims to increase the level of R&D spending in the UK from 1.7% to 2.4% of GDP by 2027. The figures for Germany and the US, by comparison, are 2.9% and 2.8% respectively.

MERCK AND QIAGEN INVESTMENTS

The government revealed the strategy at the same time as it announced that MSD (**Merck & Co. Inc.**) and Germany's Qiagen were making key R&D investments in the UK. MSD's new "state-of-the-art hub" in London, which involves the creation of 150 new research roles, would help to "ensure innovative research into future treatments for patients and pioneering medicines are completed in Britain," it said. *(Also see "Merck's UK Proposal: What's Attracting the US Giant To London For Innovation?" - Scrip, 27 Nov, 2017.)*

"Clark cited the Merck deal when asked on the BBC's Today program how much difference the Industrial Strategy would actually make, particularly in view of the challenges posed by Brexit.

"We have taken a strategic approach because we have convinced companies that we are serious about being the best place in the world. This is not just going to create jobs in the future, actually they [companies] are making those decisions now, and it is a big vote of confidence," Clark declared.

As to what the government might have said to the two companies to reassure them that all will be well after Brexit, Clark said: "The assurances we give are public assurances." As part of the Brexit negotiations, he said, "what we want to achieve is not only to continue to trade with the EU but to do more trade around the world and, working closely with these industries, it is important that we understand what they need from the negotiations." He added: "People don't make investments of this scale, which are for the long term, if they don't have the confidence that we really are building in this country a very attractive base."

The ABPI too was cheered by the news. "Today's announcement of major investment in new research and development facilities by global pharmaceutical company MSD is a vote of confidence in the strength of UK science and a signal of the government's ambition to compete on a global scale," said Thompson. For Steve Bates, CEO of the BioIndustry Association, the announcement was "great news for the UK."

Adrian Tombling, head of the life sciences group at intellectual property firm Withers & Rogers, said the news of the planned investments was "further endorsement of the fiscal and legislative measures, which are already helping to position Britain as a place to come and innovate. It is particularly positive as Brexit nears that corporates are taking up the opportunity to make strategic investments here."

"NO JLAB PLANS SHELVED" SAYS J&J

There had been rumors that Johnson & Johnson had dropped plans to establish a UK JLABS innovation center unit in Cambridge partly because of the uncertainty caused by Brexit, but the company denied this was the case. It told the *Pink Sheet*'s sister publication *Scrip* that the article in the *Daily Telegraph* was "unsubstantiated" and there had been no such deal on the table. It said it was continuing to assess opportunities for JLABS in Europe, and had not ruled out the possibility of setting one up in the UK.

From the editors of Scrip Regulatory Affairs. Published online November 27, 2017

EMA Explains How To Make Brexit-Related MA Changes, As Industry Bodies Urge Transition Period

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New guidance just issued by the European Medicines Agency shows the complexity of the procedures pharma firms will have to follow when transferring marketing authorizations (MAs) and making changes to batch release and pharmacovigilance personnel as a result of Brexit. All such changes have to be made before the Brexit date of March 30, 2019.

Companies can follow simplified procedures for certain changes, such as new manufacturing sites, and can group several Brexit-related variations in some cases, but transfers of UK MAs cannot be grouped and a separate application will be needed for each one, even where several MAs are to be transferred to the same legal entity in the EU.

The guidance was published on the same day that UK and European industry bodies joined forces to urge negotiators to agree a transitional period after Brexit, saying that otherwise companies will not be able to make the necessary changes in time.

MA TRANSFERS

The need to transfer centrally authorized MAs from the UK to a legal entity in another EU/EEA member state as a result of Brexit is a key concern for companies and regulators. Article 2 of Regulation (EC) No 726/2004 on medicinal products states that the marketing authorization holder (MAH) must be "established in the Union" which, through the EEA Agreement, is extended to include Norway, Iceland and Liechtenstein.

The guidance, which complements a question-and-answer document published by the EMA and the European Commission in May says that in order to effect an MA transfer, proof that the new MAH is established in the EEA must be provided with the transfer application. *(Also see "Change And More Change: That's What Brexit Means For Drug Companies" - Pink Sheet, 1 Jun, 2017.)* All transfers must be fully implemented before March 30, 2019.

> "One transfer application will need to be submitted for each marketing authorisation concerned" – EMA guidance

While manufacturers with numerous MAs to transfer might have hoped to be able to group them in one application, particularly where they are all going to one new legal entity, the guidance says this is not possible.

"One transfer application will need to be submitted for each marketing authorisation concerned in accordance with the current procedure provided for in Regulation (EC) No 2141/96 even in cases where several marketing authorisations are transferred from a UK-based MAH to the same Transferee," it declares. "It is not possible to group several marketing authorisations under one single transfer application."

However, a combined version of each supporting document required – except the product information and mock-up – can be created to cover all products affected. The guidance says a declaration should be included in the cover letter listing the related parallel transfer applications and confirming that the supporting documents are identical. When supportive documents differ between applications this also needs to be reflected in the statement in the cover letter."

If a product's name consists of the substance (INN/common name) and the name of the MAH, its name may need to be changed to reflect the name of the transferee. This will require a Type IA variation that should be sent to the EMA before the transfer application is made, so as to allow the product name to be reflected in the European Commission decision on the transfer. For human medicines, the name will have to be accepted by the agency's Name Review Group.

The grouping of Brexit-related variations is allowed where the grouping "does not delay implementation of changes which need to be in place by the time of UK's withdrawal from the EU," the guidance says, adding that a work-sharing application can be used in the case of identical changes applying to several products with the same MAH.

ORPHAN DRUG DESIGNATIONS

Changes will also need to be made for orphan drug designations, as sponsors established in the UK will have to be replaced with one in an EEA country "at latest by the date on which the UK leaves the Union."

A change in sponsor will result in a transfer of the orphan designation if it involves a change in legal entity, the guidance says, noting that proof will be needed that the sponsor is established in the EEA. There is no fee for a transfer of orphan designation, although

> Changes will "take a significant amount of time and will result in capacity issues which cannot be resolved before March 2019" – UK and EU industry bodies

each transfer will require a separate application.

Orphan transfer applications should be made in advance of, or in parallel with, applications for an MA transfer because "the opinion on the orphan designation transfer has to be reached before the opinion on the marketing authorisation transfer."

MANUFACTURING CHANGES

Finished product batch certification can only be performed by a qualified person of the manufacturer or importer that is identified in the MA and is located in the EEA, and the site for batch control has to be located either in the EEA or in a country covered by a mutual recognition agreement. For products manufactured outside the EEA, an authorized importation site in the EEA is needed.

This means that where products have batch release and quality control testing sites only in the UK, these will have to be moved to an EEA country. "For products that have other batch release and testing sites," the guidance says, "the MAH may choose to delete the site(s) or may choose to replace them. For finished products manufactured in the UK an importation site (in EEA) will need to be introduced."

Where changes of UK manufacturing sites are made as a result of Brexit, the guidance says that these can be submitted as a Type II variation separately for the active substance and the finished product, "thereby replacing a large grouping of Quality IB (and IA) variations for the consequential changes." If there is also a change to the UK batch release site, a Type 1A variation will be needed.

The qualified person for pharmacovigilance (QPPV) and the pharmacovigilance system master file (PSMF) must both be located in the EEA, but changes to the QPPV or the PSMF can be made simply by notifying the authorities via the Article 57 database, without the need for a variation.

Changes to the people responsible for scientific services or for batch release and quality defects should be notified in writing to the EMA.

INDUSTRY BODIES CALL FOR TRANSITION

On the same day the guidance was issued (Nov. 28), UK and European life science industry bodies again called for a post-Brexit transition period, saying that it will not be possible for companies to complete all the necessary changes before March 2019. "Even in the context of the Brexit negotiations where all sectors are looking for clarity on the future, it's important to recognise that medicines are different," they said.

The call was made in a joint statement by the AESGP and the PAGB (non-prescription medicines), EFPIA and the ABPI (R&D-based pharma firms), the BioIndustry Association and EuropaBio (biotech companies), EUCOPE (pharmaceutical entrepreneurs' confederation), and Medicines for Europe and the BGMA (generics and biosimilars).

"Whilst we respect the phased approach of negotiations, we urge progress to be made in the negotiations as soon as possible," the associations said. "We urge Brexit negotiators on both sides to agree on a transition period that adequately reflects the time needed by companies, as well as all relevant authorities at EU and national level to adapt to changes in view of the UK exiting the EU."

They added that the transition period should provide for continued EU-UK partnership on the regulation and supply of medicines to avoid supply disruptions while moving towards a future cooperation agreement.

Submitting applications for the transfer of MAs for many products, moving batch release sites and duplicating quality testing for products or moving personnel into either jurisdiction will "take a significant amount of time and will result in capacity issues which cannot be resolved before March 2019," they declared.

"Clarity and certainty are needed as early as possible to enable our industry to make the necessary changes and to transition smoothly into the new framework. This is key to ensure that there is no disruption in the supply of medicines for patients after March 2019."

Companies were recently advised by senior officials at the EMA not to bet on a transition period and to be "proactive" in making the necessary changes to their MAs. *(Also see "Betting On A Brexit Transition Period Is A Gamble: EMA Warning For Industry" - Pink Sheet, 11 Oct, 2017.)*

From the editors of Scrip Regulatory Affairs. Published online November 28, 2017

Govt Urged To Act To Forestall Medical Isotope Shortages If UK Quits Euratom

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Senior UK physicians have urged the UK government to start taking action now to ensure there is no disruption in the supply of radioactive isotopes for medical use if the UK pulls out of the Euratom nuclear community as a result of the Brexit vote.

Euratom (the European Atomic Energy Community) governs trade in radioisotopes and other nuclear technology across the EU. Although it is legally distinct from the EU, the government's position is that UK will have to pull out of the treaty because it comes under the jurisdiction of the Court of Justice of the EU.

Giving evidence to a recent hearing of the House of Lords' EU Home Affairs Sub-Committee, witnesses said that if the UK leaves Euratom, the supply of medical isotopes could be put at risk, potentially jeopardizing the treatment and diagnosis of thousands of patients across the country.

They also complained there was no sign of a unified approach to the problem from the various government ministries and departments involved. "If we leave Euratom, it is equivalent to a hard Brexit," one witness told the sub-committee. "We want more detail than just being told it won't be a problem."

Radioisotopes are widely used in medicine, both as treatment for various cancers and for imaging bones and heart muscle as well as brain, thyroid, lung and liver function.

[Brachytherapy (insertion of radioactive seeds) is used to treat various cancers, while technetium-99m is used to image bones and heart muscle as well as the brain, thyroid, lungs and liver, for example. Iodine-123 is increasingly used for diagnosis of thyroid function.]

Jeanette Dixon, vice-president of the faculty of clinical oncology at the Royal College of Radiologists, told the sub-committee that isotopes were often used therapeutically in malignant disease. "For cervical cancer, iridium is a radioisotope we use for delivering brachytherapy internally to patients, so cervical cancer is pretty much dependent on this for a cure, in combination with other types of radiotherapy."

Iodine125 is used as brachytherapy for prostate cancer, with roughly 500 procedures used each year in patient who would otherwise need to undergo an operation or who are unsuitable for surgery, she said. Around 500 more patients are given iridium for more advanced prostate cancer either as a boost to external beam treatment or used internally on its own. "So there are a lot of uses of radioisotopes in oncology," she declared.

POTENTIAL TRADE BARRIERS

John Buscombe, president-elect of the British Nuclear Medicine Society, said that isotopes were used in more than 700,000 patients a year to diagnose conditions like cancer and heart, kidney, lung and bone disease. "80% of radioisotopes are imported from outside the UK, the majority from the EU but not exclusively so, we have some imports from Australia, South Africa and the US," he stated.

The advantage of Euratom membership, Buscombe said, is that "we can transport radioisotopes without prior warning or consent… there are very significant rules and regulations on transport, import and export." Every batch of material has to be tracked from factory to patient, and in the EU single market this works well because "there are no customs checks."

Leaving Euratom would mean the UK having to create a system for radioisotopes imported from the EU similar to that currently used for material originating outside the EU, he said, and this could cause holdups at customs and border checkpoints.

To illustrate the point, Buscombe said: "Most of the radioisotopes from the EU come in a van through the Channel tunnel at night. It seems this is the quickest and easiest way, but if this is all clogged up by lorries trying to get through customs, how does my little van with my radioisotope get through, even if it is a priority product? It often comes down to practical things and how we build a system around that. We have limited time to build that new system and make sure everything is in place, and this is where our concern is."

> "If this is all clogged up by lorries trying to get through customs, how does my little van with my radioisotope get through?"
> – John Buscombe, British Nuclear Medicine Society

Moreover, there is a time factor with isotopes that doesn't apply to "normal pills and potions," Buscombe declared. "Radioisotopes decay, and the longer the delay in transporting them, the less effective they are when they arrive. "And so you need to buy more, this will cost more, let alone the tariffs that could be added to the cost, and this cost will be borne by the British taxpayer

"The UK will have to reproduce all safety checks and keep them up to date"
– Michael Rees, BMA

through the NHS [National Health Service]."

The time factor was also brought up by Michael Rees, co-chair of the medical academic staff committee at the British Medical Association, who said the best arrangement was to have supply sources as close to hospitals as possible, "which at the moment is Europe."

Rees pointed out that Euratom has a European observatory that is working towards a seamless supply of radioactive materials including medical isotopes. "If we come out and are not associated with that observatory and the European supply agency, then we are a third party and the future as far as that type of safeguard is somewhat unknown."

One longer-term alternative, Rees said, was to "generate our own isotopes" but this would not address the short-term supply problem "and we need to address it as effectively as we can."

Buscombe also sounded a note of caution regarding the domestic production and export of isotopes. For example, leaving Euratom would make things more difficult for GE Healthcare in Amersham, which is a major producer and exporter of radioisotopes. "They will be affected and it will make it more difficult for them to compete and export to Europe. If they feel they are unable to do that and would rather do that in Europe, our last home production would go, and nearly all would have to be imported."

REGULATORY DIVERGENCE, RESEARCH EFFECTS

As with the wider life sciences sector, the witnesses were also concerned over possible divergences in regulations governing the safety and quality of radioisotopes as a result of Brexit. Rees pointed out that the UK will "have to reproduce all safety checks and keep them up to date, and quality checks, and ensure that suppliers outside Europe also meet quality standards. We have reassurances from our suppliers in South Africa, but if we have to work with other countries we will have to repeat" these checks.

And for isotopes traded with the EU27 in future "there will be a continual need to update all our regulations and safety procedures to keep in step with whichever country we are dealing with."

"One risk is that these are pharmaceuticals, and as we fall out of the European Medicines Agency and become a third country there could be additional pharmaceutical barriers, and we may require more local quality assurance if we follow our own rules and regulations," said Buscombe. "If we are not safe we won't be able to trade in any radioactive goods. The worst case scenario is we are told no one can import from us."

Rees also expressed concern about funding for research into nuclear medicine. "Leaving Euratom is a significant worry for us. If you take it together with EU research programs, there isn't another research funding organization like it. Universities are net beneficiaries of money we put into the EU for research, and a great deal of UK based research is dependent on those types of programs."

He pointed out too that the nuclear medicine workforce in the UK is particularly dependent on EU doctors and that leaving Euratom could exacerbate existing staff shortages. "I think about 30% of the nuclear medicine workforce is from the EU." He said the BMA had recently surveyed of doctors from other EU countries to see what their intentions were. It found that 18% of those surveyed were intending to leave the UK, and 45% were thinking about it.

The British Medical Association's Michael Rees pointed out that the UK's nuclear medicine workforce is particularly dependent on EU doctors and that leaving Euratom could exacerbate existing staff shortages.

GOVERNMENT ACTION NEEDED

Overall, the witnesses felt that a great deal of work would be needed if the UK had to reproduce what was already in place through Euratom, and that the government needed to take action now.

Reflecting concerns expressed by many other industry sectors, Buscombe said the problem was that "we don't have a single voice within government, just multiple voices looking at their own facets. One of our pleas is to have a sort of unified approach to the problem from all the government ministries and agencies involved."

Asked whether a transition period after the UK left the EU would be of help, Rees said it would be helpful to help adjust to the future arrangements as it would "give us time and cause much less anxiety." But Buscombe said it depended on the nature of any transition period after Brexit: "If we effectively remain in Euratom, then we carry on as now, but if we leave Euratom, it is equivalent to a hard Brexit. We don't really know what the word transition means."

Noting that Jo Johnson, the Minister of State for Universities, Science, Research and Innovation, had given reassurances earlier this year that there would be no supply interruptions, Buscombe said "we would like to see how that will be done. We are getting closer to the deadline. What I would like to see now is some idea of how government agencies and ministries will put together a structure that ensures that will happen. We want more detail than just being told it won't be a problem."

From the editors of Scrip Regulatory Affairs. Published online November 27, 2017

GAO Report Casts Shade On Sunscreen Ingredients' Chances With FDA

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FDA and sunscreen active ingredient sponsors appear at a standstill on using time and extent applications (TEAs) to add ingredients to the OTC monograph, the General Accountability Office says in a report to Congress. Increased FDA resources alone aren't the sole solution to the problem, because sponsors are so far reluctant to invest in studies needed to support TEAs.

An alternative route, the new drug application process, is no more likely to attract sponsors, especially given the relatively fast evolution in sunscreen ingredients and that NDAs are for finished products, GAO's report suggests.

While the independent congressional agency's report focuses specifically on sunscreen ingredients, its analysis applies to consumer product ingredients and indications more broadly, further validating the widespread view that the OTC monograph system is currently untenable. It could bolster congressional efforts to overhaul the monograph system in tandem with creating OTC user fees, efforts that build upon FDA/industry negotiations. The revamp would include a more flexible administrative approach for FDA reviews (rather than the current rule-making process) and deadlines for agency decisions. *(Also see "Legislators On OTC Monograph Reform: What Took You So Long?" - Pink Sheet, 14 Sep, 2017.)*

The report was submitted Nov. 15 to the leadership of the House and Senate committees with oversight of FDA. It is based on interviews with drug and personal care product industry stakeholders; GAO not make policy recommendations in the report.

While sponsors could use TEAs for any consumer ingredients, the eight pending TEAs are for sunscreen ingredients. No TEAs have been approved.

While sponsors could use TEAs for any consumer ingredients, the eight pending TEAs are for sunscreen ingredients. No TEAs have been approved.

GAO compiled the report as a requirement of the Sunscreen Innovation Act. Passed in 2014, SIA imposes deadlines and timetables for FDA's review of sunscreen TEAs. *(Also see "FDA Sunscreen GRASE Final Guidance Unchanged From Draft" - Rose Sheet, 22 Nov, 2016.)* FDA has met all SIA-established deadlines, starting with advising the sponsors of the eight TEAs already pending with the agency that the proposals had insufficient data to merit evaluation and also including publishing guidance on preparing and submitting TEAs *(see table, p. 14)*

The TEA process allows proposals for adding ingredients to OTC drug monographs when they have histories of safe use in other countries, a qualification that is not evidence of safety but opens the door for considering whether an ingredient should be available in the US. Sunscreen ingredients available outside the US and proposed in TEAs include bemotrizinol, drometrizole trisiloxane and octyl triazone.

GAO states that sponsors of the eight pending sunscreen monograph TEAs said they and FDA "are essentially at a standstill" about adding more ingredients through the monograph process. Regardless of FDA's review resources, resolution "will also depend on

Lamar Alexander

Patty Murray

Frank Pallone

Greg Walden

GAO's report submitted to Senate HELP Committee Chair Alexander, R-TN, and ranking member Murray, D-WA, and House Energy and Commerce ranking member Pallone, D-N.J., and Chair Walden, R-OR, examined FDA's implementation of Sunscreen Innovation Act requirements and the status of sunscreen monograph applications.

FDA Record On Reviewing Sunscreen Monograph Applications Under SIA

REQUIREMENT	STATUTORY DEADLINE	COMPLETION DATE
Issue notice that feedback letters from FDA, sent to sponsors of some sunscreen applications prior to the enactment of SIA, are considered proposed orders.	1/10/2015	1/7/2015
Issue proposed orders for pending sunscreen applications submitted prior to SIA that did not receive feedback letters prior to SIA's enactment.	2/24/2015	2/24/2015b
Issue draft guidance for sunscreen applications on • format and content of data submissions • safety and efficacy data, • withdrawal of applications, and • use of advisory committee.	11/26/15	11/20/15
Issue first report to Congress on various performance metrics.	5/26/2016	5/25/2016
Issue final guidance for sunscreen applications on • format and content of data submissions, • safety and efficacy data, • withdrawal of applications, and • use of advisory committee.	11/26/16	10/7/2016 – 11/22/2016
Issue second report to Congress on various performance metrics.	5/26/18	Pending
Finalize sunscreen monograph.	11/26/19	Pending
Issue third report to Congress on various performance metrics.	5/26/20	Pending

Source: GAO report, Nov. 15, 2017

sponsors and other interested parties submitting data that FDA determines are sufficient for" determination as generally regarded as safe and effective.

But TEA sponsors' margin for error is too wide while their margin for profit is too narrow to support conducting the additional tests requested, GAO reports.

No sponsor of any of the eight pending TEAs had submitted additional information to FDA when GAO completed its review. The report says "the sponsors are either still considering whether to conduct the additional tests … or they do not plan to do so." The gridlock could encourage sponsors instead "to devote their resources into developing a newer generation of sunscreen active ingredients."

Absent complete restructuring of the overall monograph process, sponsors of applications shouldn't expect success, says regulatory consultant David Steinberg. He warned that frustrated sponsors could decide the "US market is pretty well closed" for now. He is president of Steinberg & Associates Inc., a Plainsboro, N.J., consultancy specializing in the OTC drug and personal care industries.

The Personal Care Products Council, one of the stakeholders GAO contacted for the report, isn't quite as pessimistic. Chief Scientist Beth Jonas says the trade group agrees "with the overall findings … that there are significant obstacles hindering" approval of new ingredients but wouldn't say that all work on making additional sunscreen ingredients available has been paused.

"The FDA has indicated the information it would like to receive, and sponsors interested in obtaining new sunscreen filters in the US are continuing to engage with relevant stakeholders," Jonas said. The council represents a number of firms that market sunscreen products.

The Consumer Healthcare Products Association, representing OTC drug manufacturers including several that market sunscreens, also says potential remains for firms to make progress under the current monograph system.

"But until FDA receives more data from sponsors, as requested, there is unlikely to be any more movement on the new ingredient applications," said Barbara Kochanowski, CHPA's senior vice president for regulatory and scientific affairs, in an email.

ROI, MUST AND ANIMALS

Still, sunscreen firms say the testing FDA requested is "would cost millions of dollars" and take multiple years to complete, GAO re-

Sponsors are concerned that spending on MUsT tests will not lead to TEA approval, or that FDA then would ask for still more and different trials.

ported. And unlike drug products granted some market exclusivity when they're approved through NDAs, ingredients added to an OTC monograph can be used immediately by firms across the industry.

FDA's insistence on "maximal usage trials" (MUsT) and for the absorption tests it requests while rejecting alternatives also dissuades the TEA sponsors from proceeding, GAO found. Although the sponsors say they are not aware of MUsT pharmacokinetic tests being conducted on sunscreen ingredients and there is little information available on how to conduct this test, FDA officials said it is a test that has been used for dermal products since the 1990s.

Sponsors are also concerned that spending on MUsT tests will not lead to TEA approval, or that FDA then would ask for still more and different trials, the report states.

Additionally, sunscreen ingredient firms question FDA's request for nonclinical animal studies to characterize potential long-term dermal and systemic effects of exposure to an ingredient. Conducting animal studies on ingredients could limit the number of countries where a firm could market a sunscreen while also prompting animal rights advocates' protests in countries where the practice is not prohibited.

Driving FDA's insistence that additional information, particularly on absorption into the skin, is needed in the pending sunscreen TEAs is CDER officials' determination that sunscreens currently are used more regularly than when the existing monograph ingredients were approved.

GAO's report says industry stakeholders understand FDA's argument, but also contend the agency should give more weight to the benefit of better sunscreen ingredients being available.

NDA IMPEDIMENTS HIGH, INCENTIVES LOW

Regarding the NDA route, sunscreen ingredient firms say the process is too costly and a product approved through the process is eligible for market exclusivity only when FDA requests clinical trials as part of the application. In the GAO report, industry stakeholders say firms could incur recurring NDA costs for products made with the same ingredient but with varying formulations, such as different fragrances.

The stakeholders contacted for the report said "NDAs are impractical for sunscreen products, because the formulations are continually changing," according to GAO.

Another factor that weighs against using the NDA pathway is that some sponsors of monograph sunscreen applications are ingredient manufacturers that don't make finished products, which are what FDA evaluates.

From the editors of the Tan Sheet. Published online November 27, 2017

FDA's NDA And BLA Approvals: Impoyz, Clenpiq

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				
Promius	*Impoyz* (clobetasol propionate)	Corticosteroid cream to treatment moderate to severe plaque psoriasis in patients 18 years of age and older.	S, 5	11/28/2017
Ferring	*Clenpiq* (sodium picosulfate/magnesium oxide/anhydrous citric acid)	10 mg/3.5 g/12 g oral solution of the ingredients which form magnesium citrate, an osmotic laxative, indicated for cleansing of the colon as a preparation for colonoscopy in adults.	S, 3	11/28/2017

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

US FDA Issues Long-Awaited DSCSA Grandfathering Guidance

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The pharmaceutical industry has much needed clarity now that FDA has finally spelled out its criteria for allowing un-serialized or 'grandfathered' drug products in the pharmaceutical distribution chain under the 2013 Drug Supply Chain Security Act.

The policy was announced in a draft guidance document, "Grandfathering Policy For Packages And Homogenous Cases Of Product Without A Product Identifier," issued on Nov. 27, the day DSCSA began requiring manufacturers to affix serial numbers to their products.

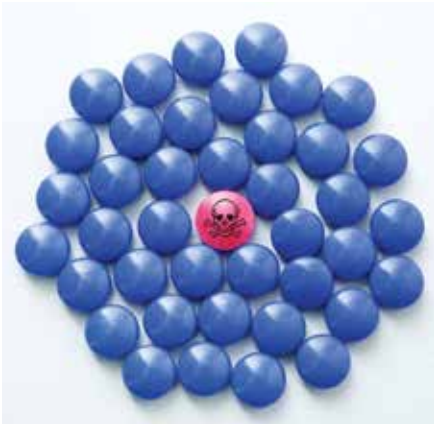
A compliance policy guide FDA issued in June responded to industry complaints by giving manufacturers an extra year to comply before the agency would penalize them for failing to meet the Nov. 27 deadline. *(Also see "FDA Gives Drug Makers One-Year Reprieve From DSCSA Product Identifier Requirement" - Pink Sheet, 30 Jun, 2017.)*

The draft guidance clarifies that a package or homogenous case of product that is not labeled with a product identifier will be exempt from serialization requirements if there is documentation that it was packaged by a manufacturer before Nov. 27, 2018.

For example, if a package or homogenous case of product not labeled with a product identifier is accompanied by transaction information or a transaction history that includes a sale before Nov. 27, 2018, that trading partner can "reasonably conclude that the product was packaged by a manufacturer before that date."

Industry had wanted clarity on when products are considered grandfathered, and FDA was two years late issuing guidance on this issue. The November 2013 law required FDA to issue guidance by November 2015 defining grandfathering and how to obtain waivers, exceptions and exemptions from the serialization requirement.

Just a few weeks earlier at a meeting sponsored by the Food and Drug Law Institute, FDA's Ilisa Bernstein announced a further delay in issuing a guidance on grandfathering to give the agency time to review industry's comments on the CPG. FDA said in the CPG that it planned to issue additional guidance "that will outline FDA's current thinking on the 'grandfathering product' provision."



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> The draft guidance clarifies that a package or homogenous case of product that is not labeled with a product identifier will be exempt from serialization requirements if there is documentation that it was packaged by a manufacturer before Nov. 27, 2018.

Industry had warned FDA in its comments on the CPG that the continued lack of guidance on its criteria for downstream trading partners accepting "grandfathered" un-serialized drug products by the Nov. 27, 2017, DSCSA deadline could lead to chaos. *(Also see "FDA's Delay Issuing DSCSA Grandfathering Guidance Creating Problems For Manufacturers" - Pink Sheet, 24 Nov, 2017.)*

Key industry stakeholders including the Biotechnology Innovation Organization have been operating with the understanding that the serialization obligations under DSCSA Section 582(b)(2)(A) were tied to the date the product was packaged.

Most of FDA's regulatory guidance merely consists of non-binding recommendations on a topic except to the extent that it cites regulatory or statutory requirements.

However, the grandfathering guidance is different because, as it explains, Congress authorized FDA in Section 582(a)(5)(A) of the Food, Drug & Cosmetic Act to specify "whether and under what circumstances packages and homogenous cases of product that are not labeled with a product identifier and that are in the pharmaceutical distribution supply chain at the time of the effective date of the requirements of section 582 shall be exempted from the requirements of section 582."

The guidance adds that if grandfathered packages and homogeneous cases of product are returned in saleable condition, manufacturers can later redistribute them without adding product identifiers.

The deadline for public comment is Jan. 26, 2018. Comments can be submitted to https://www.regulations.gov/docket?D=FDA-2017-D-6526.

From the editors of the Gold Sheet.
Published online November 27, 2017

Biocon, Dr Reddy's Might Be Out Of The Woods On GMP Issue

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Two Indian firms seeking to set right compliance deviations at their sites appear to have made notable gains. **Biocon Ltd.** and **Dr. Reddy's Laboratories Ltd.** have received establishment inspection reports [EIRs] from the US Food and Drug Administration at their sites in Bangalore and Duvvada respectively in India.

The EIR for the Biocon's aseptic drug product facility states that the inspection stands closed, though the FDA has classified the outcome of this inspection as VAI (voluntary action indicated), Biocon said.

A VAI inspection classification usually suggests that objectionable conditions or practices were found that do not meet the threshold of regulatory significance. Inspections classified with VAI violations are typically more technical violations of the Federal Food, Drug, and Cosmetic Act .

Industry experts maintained that while an EIR, with a VAI classification, is considered generally positive, firms need to monitor compliance issues closely to ensure no repeat deviations or unsatisfactory implementation of corrective and preventive actions (CAPAs).

Biocon's chair Kiran Mazumdar Shaw was reported in a television interview as saying that if the CAPAs are not carried out in a satisfactory way, the FDA can "come down on you in terms of observations and 483". A Form 483 is a notice of the US FDA's inspectional observations that lists deficiencies in the quality system.

"We are confident that we have implemented most of the CAPAs," Mazumdar Shaw added in the interview.

REGULATORY TRANSPARENCY

In the case of Dr Reddy's Duvvada unit in Visakhapatnam, the company said that the FDA had explained that it had released the EIR in order to be "transparent about its regulatory process" but that the inspection had not been closed and the site's status "remains unchanged".

The FDA rider is perhaps significant given that EIRs are generally provided when no enforcement action is contemplated, or after enforcement action is concluded. An EIR typically includes, among others, the investigator's narrative report and any refusals, voluntary corrections, or promises made by the firm's management.

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> "We are confident that we have implemented most of the CAPAs," Mazumdar Shaw, Biocon

"We are planning to request a re-inspection in 2018 after further discussion on scheduling with the FDA," Dr Reddy's said in a filing with the Bombay Stock Exchange on Nov 21.

Nimish Mehta, founder of Research Delta Advisors, told the *Pink Sheet* that the FDA was, in general, becoming more "transparent and communicative" when it comes to the good manufacturing practice (GMP) status of sites.

Mehta noted that the US Generic Drug User Fee Amendments (GDUFA) II refers to how by Oct. 1, 2018, the FDA expects to communicate to the facility owner final inspection classifications that do not negatively impact approvability of any pending application within 90 days of the end of the inspection. As per the GDUFA II commitment letter, the FDA has also agreed, among other aspects, to ongoing periodic engagement with industry stakeholders to provide updates on agency activities and seek stakeholder feedback.

"The Dr Reddy's EIR perhaps suggests that it is unlikely that there will be any further escalation in issues at Duvvada. But the ball is clearly in the company's court," Mehta said.

The Duvvada unit had earlier failed to make the cut in an audit by the German regulator. *(Also see "Another Dr Reddy's Plant Runs Afoul Of German Regulator" - Pink Sheet, 11 Sep, 2017.)*

BIOCON'S EIR

The stakes appear rather high for Biocon, given that the Bangalore site caters to firm's biosimilars pipeline.

The EIR comes just weeks before the extended Dec. 3 FDA target action date for Biocon and partner **Mylan NV**'s biosimilar trastuzumab 351(k) application. The extension of the target action date from Sept. 3 was essentially to review "some of the clarificatory information submitted" to the agency as part of the application review process, Biocon had indicated in August.

"This three-month extension has no impact on the anticipated timetable for commercialization of this product in the US," the Bengaluru-based firm maintained at the time.

A Biocon statement said that the latest EIR pertained to the cGMP (current GMP) inspection of its aseptic drug product facility that was audited between May 25 and June 3. The company declined to comment any further, including whether the FDA's previous concerns on inadequate data – seen as a prickly area by some analysts in terms of inspectional outcomes – have been successfully addressed.

The FDA inspection at Biocon's Bommasandra, Bangalore, site conducted between May 25 and June 3 had earlier listed several deviations including deficiencies in the aseptic processing area and inadequate laboratory controls. The agency had, at the time, also noted that laboratory records at the Bangalore unit did not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

Biocon did not clarify whether the drug substance facility at the Bangalore site would need separate FDA clearances. A pre-approval inspection by the FDA between March 27 and April 7 this year pertaining to the firm's drug substance and drug product manufacturing unit there had flagged up compliance deviations. *(Also see "FDA Inspection Yields Insight Into Biocon/Mylan Biosimilars Manufacturing Challenges" - Pink Sheet, 11 Jul, 2017.)*

RUB-OFF ON EMA INSPECTION OUTLOOK?

It's also unclear if the developments on the compliance front with the FDA could improve the outlook for inspections by the European Medicines Agency for the two firms. This is especially so in the general backdrop of the coming into operation of the mutual recognition agreement between the EU and the US to recognize inspections of manufacturing sites for human medicines conducted in their respective territories. *(Also see "US/EU Agreement Will Reduce Global Import Testing Burden" - Pink Sheet, 2 Nov, 2017.)*

Biocon and Mylan had earlier retracted applications for their biosimilar versions of trastuzumab and pegfilgrastim in the EU in the backdrop of manufacturing compliance lapses. *(Also see "More Questions As Biocon Pulls EU Filings For Two Biosimilars" - Pink Sheet, 16 Aug, 2017.)* A pre-approval inspection by the French regulator, ANSM, had earlier flagged compliance deficiencies at Biocon's Bommasandra site for three biosimilars – pegfilgrastim, trastuzumab and insulin glargine and the Indian firm had, at the time, indicated that it would require a re-inspection of the "drug product" facility.

Earlier this month, Mylan resubmitted the marketing authorization applications for biosimilar trastuzumab and pegfilgrastim with the EMA. Biocon, at the time, said that it had completed the CAPAs, including the facility modifications, in response to the audit observations and expects these to be verified during re-inspection.

Published online November 24, 2017

Labeling Updates For Old Drugs Could Be Faster Under Streamlining Proposal

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A streamlined pathway for adding important data to labeling of older drug products could encourage submission of more labeling supplements to better reflect products' current clinical use, but the idea seems to lack strong support from the US FDA and the generic drug industry due to a host of factors including complexity, resources and product liability concerns.

The proposal, aimed at bringing labeling for older drugs into line with current real-world practice, was introduced at the Friends of Cancer Research's (FOCR) recent annual meeting in Washington, DC. Described as a "straw man" because it was intended to generate discussion, the concept was developed by a multi-stakeholder group encompassing cancer patient advocates, clinicians, and legal experts.

Although FDA and the Association for Accessible Medicines (AAM) reviewed and commented on the draft discussion paper, they were not signatories.

The paper describes a pilot program aimed at correcting out-

When an NDA for a reference listed drug is withdrawn, leaving only generic versions on the market, "it basically freezes the label at least as far as the indications go." – FDA's Woodcock

dated labeling that does not reflect a drug's current use in clinical practice, either because the brand sponsor responsible for the reference product has no incentive to add a new indication or seek a labeling change, or because the reference listed drug has been withdrawn and only generic versions remain on the market.

OUTDATED LABELING VEXES FDA

The issue of outdated product labeling has long been a concern to the agency, Center for Drug Evaluation and Research Director Janet Woodcock said at the FOCR meeting.

In therapeutic settings outside of oncology, reimbursement is often tied to a drug's labeled indication, she noted. In addition, "we are concerned … as these labels get way out of date some practitioner who isn't usually in the field but wishes to use that drug reads the label and gets inaccurate instructions [or] does procedures that are no longer necessary, uses incorrect dose."

Perhaps the biggest challenge to ensuring that labels stay current is when a reference listed drug sponsor withdraws its new drug application (NDA), leaving only generics on the market. Since generics must have the same labeling as the reference product, when an NDA is withdrawn "it basically freezes the label at least as far as the indications go," Woodcock said.

"We have over 450 drugs … that don't have any innovator marketing. It's just the generics that are on the market," Woodcock said. "That label has caused us a lot of problems even approving the generics. It's hard for us to overtly approve a new generic drug when we know the label is wrong in some way."

Although FDA has authority to order safety-related changes to labeling even if a reference listed drug has been withdrawn, "changing substantial information in the generic label without a reference sponsor to negotiate with is difficult," Woodcock said. "We couldn't add indications."

STREAMLINING THE SNDA ROUTE

The proposal discussed at the FCOR meeting calls for FDA to identify products that have been on the market for at least 15 years and for which labeling lacks either critical efficacy or safety information or contains incorrect or misleading prescribing instructions.

FDA would notify the sponsors of the affected drugs to seek agreement to pursue revised labeling. The agency would then work with stakeholders to review the available postmarketing evidence, and this could entail cooperative agreements or contracts with private entities to conduct an evidence review.

Based on this evidence review, FDA would determine whether the data meet the approval standard for a labeling revision and, if so, publish a notice in the Federal Register summarizing the data and inviting the reference listed drug sponsor or abbreviated new drug application (ANDA) holders to submit labeling supplements under Section 505(b)(2). FDA would approve the sNDA as the reference drug, and all other generic labeling would be updated to reflect the changes.

Josephine Torrente, a director at Hyman, Phelps and McNamara and one of the contributors to the draft discussion paper, said the proposal "is the simplest way we could think of that involved the least cost and the least effort."

However, she acknowledged limitations to the proposal, including that there is no financial incentive for either an NDA holder or an ANDA holder to request a labeling update for an older product because additional exclusivity would not be available. "It's really a good citizen motive," she said. "I don't know how much incentive is needed for that."

Additionally, if an ANDA holder is the entity that pursues a labeling change and becomes the new reference drug, it potentially could open the door to failure-to-warn claims related to that product, Torrente said, suggesting that a legislative fix may be needed to address such product liability concerns.

"The current proposal is theoretically doable under the existing authorities," she said. "I think the issue is that we may find that either there's not sufficient money to do it, to have people pull the data together convincingly, or there's not sufficient incentive to generic companies or innovator companies to do it."

When it comes to incentive, "I think legislation would be, if not needed, certainly helpful to deal with some of the issues that are in the way and either create carrots or sticks to encourage this to happen," she said. "I don't think it's necessary legally, but it may be necessary practically."

AAM HAS RESERVATIONS

Rachel Sher, AAM's deputy general counsel, expressed the generic drug trade association's support for the proposal's goal but raised concerns that even such a streamlined process may be too burdensome or expensive for generic manufacturers. She also raised liability issues and questioned how it would impact generic substitution practices.

"We support the goal of the white paper and stand ready to be a partner in what I think is a very complicated task," she said.

While AAM supports making updated information about drugs available in a timely fashion, labeling is only one way of conveying such information and "it's definitely not the only way or even the

The proposed piloted program "is theoretically doable under the existing authorities." – Hyman Phelps' Torrente

FDA said it terminated the PDLI-EI contract "because of the complex scientific, legal and regulatory considerations associated with updating older labeling identified during a pilot phase."

most frequently used particularly in clinical practice," she said.

When NDAs are withdrawn, in many cases FDA has taken leadership in directing generic drug labeling changes, which ensures the accuracy and consistency of product labeling, Sher said. "AAM fully supports this model and believes that this is the best way to get timely information to patients and their providers."

CDER'S UNHAPPY PDLI-EI EXPERIENCE

CDER's Woodcock also expressed reservations about the proposals based in part on experience several years ago with the Prescription Drug Labeling Improvement and Enhancement Initiative (PDLI-EI), a pilot project to identify best practices and standardize the approach to voluntary conversion of older product labels into the Physician Labeling Rule (PLR) format.

A Feb. 6, 2013 Federal Register notice described the agency's plans to use a contractor to provide PLR conversion resources and services, including preparation of draft PLR labeling, for applicants who request FDA's assistance to convert older drug labeling to PLR format. The plan called for FDA to review the draft labeling prepared by the contractor and then send the applicant the proposed draft PLR format labeling, and the applicant would submit a labeling supplement to FDA. *(Also see "FDA Wants All Drug Manufacturers To Adopt Highlights Labeling Format" - Pink Sheet, 5 Feb, 2013.)*

Woodcock said the agency hired a contractor "to try to clean up a couple of really old labels that were really a mess and they didn't even at all reflect how the drugs were being used nowadays. And what we got back we couldn't use, so then we cancelled the contract."

"It makes me realize what FDA does there's kind of an art to it, and there may not be that many people who understand all the standards and all the things you have to go through," she said.

Because agency staff expended considerable effort on PDLI-EI, "there isn't a lot of enthusiasm for trying that route again," Woodcock said. "Of course … I'd be open to trying again if we thought that would help in this situation."

In response to questions from the Pink Sheet, FDA said it elected to terminate the PDLI-EI contract "because of the complex scientific, legal and regulatory considerations associated with updating older labeling identified during a pilot phase."

"FDA remains committed to ongoing efforts to optimize the utility of prescription drug labeling," the agency said, noting it continues to publish guidance documents related to procedural and content issues for labeling. These include a July 2016 draft guidance on updating ANDA labeling after the NDA for a reference listed drug has been withdrawn.

"The number of FDA staff dedicated to labeling review has been increased in recent years, and FDA continues to perform stakeholder outreach with opportunities such as joint FDA-industry conferences on enhancing the quality of FDA prescription drug labeling," the agency said.

Speaking from the audience at the FOCR meeting, Richard Pazdur, director of FDA's Oncology Center of Excellence, said one of the problems with PDLI-EI was that the contractors were not subject content experts, at least with regard to oncology.

"This could be done if you get the right people here," Pazdur said. "I think many of the senior people may not want to do this in the FDA, but if you made it kind of a joint project where it's more of an educational process by involving the community more, this I think you could get some traction on it."

"We would have no problem writing [proposed labeling] eventually if we had adequate resources but then … this protection from suits for the generic industry would have to be resolved," Pazdur said.

Published online November 28, 2017

The End Of 'Regulatory Science' At US FDA – The Term, Not The Idea

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The directors of the US FDA's drug and biologic centers really don't like the term "regulatory science."

Center for Drug Evaluation & Research Director Janet Woodcock and Center for Biologics Evaluation & Research Director Peter Marks made their feelings known during a panel discussion as part of the Prevision Policy/Friends of Cancer Research Biopharma Congress Nov. 14.

During a discussion of the current regulatory climate at FDA and ideas to build on the strong performance of new drug review teams, session moderator Jeff Allen (CEO of Friends of Cancer Research) mentioned "regulatory science" during a question about efforts like the Critical Path Initiative and their impact on FDA's performance.

Woodcock took the opportunity to make clear that she does not consider the term helpful in advancing the goals she has long championed for advancing translational research via collaboration. Marks followed up by agreeing that that term is too broad and vague to be useful.

"Advancing Regulatory Science," of course, was a signature initiative of the tenure of former FDA Commissioner Margaret Hamburg, who launched a formal initiative by that name shortly after joining the agency in 2010. *(Also see "Hamburg Outlines The Potential Of Regulatory Science Investment" - Pink Sheet, 11 Oct, 2010.)* Nearly three years after Hamburg left FDA, it still lives on, at least in the form of a dedicated landing page within FDA's website.

'A LOT OF PROGRESS HAS HAPPENED'

So it was somewhat surprising for Woodcock to react to the term like it was fingernails on a chalkboard. "As you know, I don't like the term 'Regulatory Science,'" she began. "The intent [of the Critical Path Initiative] was to make the community wake up and realize there is a big gap. You have to do translational science. You can't just do basic science. … This takes a long time."

"In the early 2000s … the only people who understood that other than the FDA was the companies, and they were so secretive with everything, there was no sharing of information," Woodcock said. So the idea was "to get a body of knowledgeable people and researchers going who understood what needs to get done."

"A lot of progress has happened," she added, citing specifically the C-PATH safety biomarkers initiative, which involves two dozen companies pooling preclinical safety markers. So "it has been successful, whatever they call it."

"If they want to call it 'Regulatory Science' that's – well, it's not alright with me, but that's what they are going to call it," she said.

'A WASTEBASKET TERM'

"Janet, we are in unison here," Marks added. "Regulatory Science" has "become a wastebasket term." He particularly objected to the confusion between "science" and "policy" that he thinks the term engenders.

"I went to a meeting and this guy handed me his card and said, 'I'm the head of the Institute of Regulatory Science,'" Marks said. "I started to talk to him and he looked at me like I had three heads. Because he was a policy wonk. He didn't do anything that I considered regulatory science."

"We should speak about what we are talking about. We do applied scientific research at our center. We might do a touch of basic science because you just wander into it sometimes, but the goal is to do applied scientific research that actually makes a difference directly to the products that we regulate."

"Then there is the statistical and epidemiological research that we do which is very important. Statistical methods to come up with ways to streamline small trials and draw a statistical inference from them or to use real world evidence," he said, as well as "epidemiologic data to make sure that the products we regulate are actually safe in large populations."

"Naming them makes more sense than this wastebasket term," Marks said. "Policy is really important, don't get me wrong, it really is. But we do a disservice to policy when we just lump it in this mess."

From the editors of the RPM Report.
Published online November 28, 2017

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Patient selection criteria and clinical trial design features, including acceptable endpoints, for demonstrating clinical benefit for drugs intended to treat interstitial cystitis and bladder pain syndrome; also, discussion of whether bladder pain syndrome and interstitial cystitis reflect overlapping or different populations, and whether it is appropriate to assess efficacy in the same way for both conditions	Bone, Reproductive and Urologic Drugs	Dec. 7
Clarus Therapeutics' oral testosterone undecanoate capsules for testosterone replacement in males for conditions associated with a deficiency or absence of endogenous testosterone: primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired)	Bone, Reproductive and Urologic Drugs	Jan. 9
Lipocine's oral testosterone undecanoate capsules for testosterone replacement in males for conditions associated with a deficiency or absence of endogenous testosterone: primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired)	Bone, Reproductive and Urologic Drugs	Jan. 10
Aradigm Corp.'s ciprofloxacin dispersion for inhalation for treatment of non-cystic fibrosis bronchiectasis patients with chronic lung infections with *Pseudomonas aeruginosa*	Antimicrobial Drugs	Jan. 11

Pink Sheet

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