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US Pharma Firms Warn 'Hard' Brexit Will Impact UK Investments; Clinical Trials A Casualty Of Uncertainty

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The American Pharmaceutical Group, which represents some of the major US pharmaceutical multinationals, has warned that a "no-deal" Brexit could hit UK investments by its member companies, "dramatically affect the attractiveness of the UK trading environment," and result in "extremely high" restructuring costs as a result of additional regulatory and trade hurdles.

Meanwhile, a leading UK clinical research institute has warned that the uncertainty over the final outcome of the Brexit negotiations is already leading sponsors to omit the UK from their trial plans and to no longer invest there.

> "It is imperative that as Brexit progresses no unnecessary barriers are put in place which have the potential to impact on this investment" – American Pharmaceutical Group

The comments were made in written evidence to the House of Lords Science and Technology Committee's inquiry into the UK life sciences and industrial strategy, which heard similar warnings about Brexit from the chief executives of the Association of the British Pharmaceutical Industry and the BioIndustry Association at a committee hearing last week. *(Also see "Brexit Hits Life Science Investment Decisions As UK Risks Exclusion From Key EU Projects" - Pink Sheet, 25 Oct, 2017.)* Dozens of stakeholders from all parts of the life science sector have made submissions to the inquiry.

US INVESTMENTS AT RISK

The APG, which represents AbbVie, Amgen, Biogen, Bristol-Myers Squibb, Celgene, Gilead, Janssen, Lilly, MSD and Pfizer, says that a "no-deal" scenario would also cause interruptions to the supply chain and threaten patient access to new medicines.

"As a global industry," it says, "the uncertainty of Brexit will add to the pressure of our international competition, as companies decide on their future investment in the UK." It continues: "We are clear that not only will a 'no-deal' scenario for the life sciences sector have a major detrimental effect on the UK economy, but it will also threaten access to medicines and the position of the NHS [National Health Service] as a world leading health service. If the government is to meet its ambitions for the sector, it is essential that it takes Brexit considerations into account as Ministers

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Orphan Drug Tax Credit Defense Adds To NORD's Legislative Challenges

https://pink.pharmaintelligence.informa.com/PS121894

Republican tax reform proposal would eliminate research credit; NORD already had its hands full countering 'misinformation' about impact of orphan drugs on drug spend; critics on Capitol Hill argue sponsors are gaming the system

Four Biosimilar Pegfilgrastims Under EU Review After Sandoz Re-Submits Zioxtenzo

https://pink.pharmaintelligence.informa.com/PS121880

The EMA's scientific committee, the CHMP, now has four biosimilar versions of Amgen's neutropenia drug Neulasta (pegfilgrastim) under review, after Sandoz re-submitted its product at the end of October.

Biosimilar Development Meetings At US FDA Not Just For Talking Similarity

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Sponsors shouldn't wait until pre-submission meetings with the agency to discuss manufacturing, packaging and other matters unrelated to similarity data, FDA's Leah Christl says in remarks seemingly aimed at calling attention to issues that can forestall approval.

'Bridging' Of Generic Review Goal Dates Makes Progress At US FDA

https://pink.pharmaintelligence.informa.com/PS121892

Assigning official goal dates to ANDAs that hadn't been included in GDUFA began in mid-October and already has lead to approvals.

Generic Price-Fixing Lawsuit Grows As More Companies, Two Executives Named Defendants

https://pink.pharmaintelligence.informa.com/PS121873

US state attorneys general name executives from Mylan and Emcure as defendants, and list may further expand as investigation continues into additional companies and drugs.

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develop their long-term policies."

Noting that the US overall is "the largest investor in the UK" with industry investments of "nearly $600bn in the British market," it says it is "imperative that as Brexit progresses no unnecessary barriers are put in place which have the potential to impact on this investment."

It says that in the life sciences area, the relationship between the UK regulator, the MHRA, and the European Medicines Agency (which is having to relocate from the UK to another EU country) "gives British industry access to a market of 500 million people and has made the MHRA a respected leader in regulation." For multinational pharmaceutical companies launching new medicines, their focus is on the largest markets, which currently include the EU alongside the US and Japan, according to the APG.

UK TO BACK OF QUEUE?

Outside the EU, the UK would "risk falling to the back of the queue" and being "seen as a 'secondary market', which not only heavily impacts the attractiveness of the UK market, but centrally, risks imposing longer delays on access to the most innovative treatments for patients," the APG states.

As for potential trade barriers, it says that the success of the UK life science sector has been "built on a platform of European arrangements which allow industry to transport tens of thousands of live medical compounds across the Channel a day without customs checks. The EU is a major trading partner, taking 44% of UK life sciences exports in 2015."

If Brexit were to result in "complex import/export declarations and inspections coupled with high customs and tariff fees," this would "dramatically affect the attractiveness of the UK trading environment," it declares.

The UK must therefore maintain, as closely as possible, the trading terms currently associated with EU membership to allow the frictionless free movement of medicines and pharmaceutical supplies across borders, the APG states. "If no deal or transitional arrangements are agreed, the restructuring costs resulting from the regulatory and trade hurdles will be extremely high."

Similarly at risk in a "no-deal" scenario would be companies' ability to recruit European scientists to the UK, which could "stifle growth, putting at risk the investment of £792 million in research and development made annually by APG members."

> "The uncertainty has proved damaging, with sponsors dropping out of trials and deciding not to invest in the UK" – Richmond Pharmacology

The UK government should therefore prioritize the life sciences industry as it develops a specific immigration policy, the APG recommends. "Without a route for international talent, the government will struggle to meet its aim of becoming a global life sciences leader."

CLINICAL TRIAL WORRIES

A perspective on the problems Brexit could bring to the clinical trials area was submitted by Richmond Pharmacology, a UK clinical research institute, which claims sponsors are already pulling back from investing in UK trials.

It says that the UK's decision to leave the EU has already prompted concerns and uncertainty over how UK biopharmaceutical services can compete globally, "especially if single market membership and EMA regulations are not part of the Brexit deal." The uncertainty "has proved particularly damaging, with sponsors dropping out of trials and deciding not to invest in the UK," it says.

The future relationship between the EMA and the MHRA will determine the commercial attractiveness of the UK for investment and the speed of clinical trial authorization. With the EMA based in London, the UK – through the MHRA – has "increased influence over its policy direction," Richmond says. "In return, the EMA benefits from the MHRA's expertise. Brexit endangers this as the EMA will be moving to another EU country, and consequently weaken the view of the MHRA as a life sciences hub."

At present, says Richmond, the UK is the most popular location for Phase I clinical trials in Europe, second for Phase II, and third for Phase III. This "privileged position is unlikely to continue if the UK must enact separate verification in addition to the existing European authorization," it declares.

Read the full article here

It also notes that in exiting the EU, the UK "will no longer benefit" from the streamlined portal and database system that will be introduced (in 2019) by the EU Clinical Trial Regulation, which the UK "heavily influenced" and which seeks to "better balance innovation and risk." *(Also see "Delay Means New EU Clinical Trial Rules May Not Be Transferred To UK" - Pink Sheet, 17 Oct, 2017.)*

It is essential, it says, that applications for authorization of early-phase clinical trials and their maintenance through the portal and database are "as fast, easy and efficient as the equivalent process in Europe. We need reassurance that access to the portal is a priority in the negotiations, and clarity on the cost of access to it after Britain leaves the EU."

There is also a need to ensure that Brexit does not limit access to skilled workers from overseas, Richmond says, noting that the UK "is reliant on migrant labour to attract the requisite talent for research and innovation."

While there are "undoubtedly some big questions left to answer over Brexit," the government still has a significant opportunity to promote the UK's excellence in early-phase research, it says. "The recent publication of the Government's Life Sciences Strategy did provide some reassurance through the commitment to increased R&D spending and the focus on increasing the number of clinical trials in the UK over the next 5 years by 50%."

QUINTILES FEARS GROWTH SLOWDOWN

Concerns about Brexit have also been expressed by the CRO, QuintilesIMS, which says that "the nature of our business relies on market certainty, strong regulatory standards, and close international collaboration," and has analyzed a number of

possible scenarios.

There is a "potential upside" of Brexit, it says, "driven by ring-fencing PPRS [Pharmaceutical Price Regulation Scheme] rebates for spending on innovative drugs, accelerating NHS access and uptake of new drugs."

Its baseline case suggests that funding gaps will be plugged but there will be a squeeze on public sector resources – the assumption here is that the MHRA will "align itself with the EMA" and that a new UK-EU relationship will cause "minimal disruption" to industry in general.

But its downside case suggests "more significant curtailing of pharmaceutical spending growth" than in the baseline scenario, as well as a greater risk of product shortages due to the depreciation of sterling and the possible emergence of new trade barriers. It says its analysis suggests that Brexit "could decelerate UK pharma growth over the next three years."

With regard to the EMA, it recommends that the UK "prioritize negotiating membership or associated status in this critical agency to avoid any delays to licensing applications and the recognition of qualified persons." It should also "ensure the continued free movement of biological samples across borders within the European Union to allow continuing operations of our laboratory in Edinburgh."

> "Any changes to the regulatory framework will create barriers and additional complexity for global organizations" – Novartis

There is a danger that the UK's regulatory pathway could diverge from the EU which, "when coupled with the UK's tough pricing and reimbursement environment, would lead commercial decisions to delay new product launches in the UK."

MULTIPLE UNCERTAINTIES, SAYS NOVARTIS

For the Swiss-based multinational Novartis, the long-term impact of Brexit on the life sciences industry and on Novartis itself is still unclear "as there remain numerous uncertainties which affect our business on multiple fronts." In its submission, the company "implores the Government to provide a greater level of detail on these issues as soon as possible," saying it is "keen to work with the Government to ensure that the UK's relationship delivers for patients, the NHS, and our industry."

Any changes to the regulatory framework, particularly with regard to drug approvals and intellectual property, will create barriers and additional complexity for global organizations that have set up in the UK, Novartis observes.

"It is our position that many of the core tenets that uniquely position the existing regulatory framework which afford earlier access to more innovative treatments should be preserved as much as possible following the negotiations."

It says that "strong collaboration between UK and EU agencies is something we would like to see continue following the negotiations especially in the context of a more European-centric regulatory framework that is likely emerge with the relocation of the European Medicines Agency to be confirmed later this year" [on Nov. 20).

From the editors of Scrip Regulatory Affairs. Published online November 1, 2017

Brexit Already Affecting UK Regulator's Role In Marketing Authorizations

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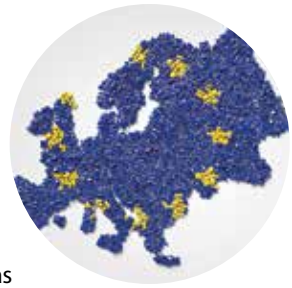

Brexit is already taking its toll on the UK as a key player in the EU regulatory network after the European Medicines Agency confirmed that the UK will now only be considered as rapporteur for initial centralized approval applications if the evaluation procedure can be completed before the country leaves the EU at the end of March 2019.

Given that it can take around more than a year to complete a new drug evaluation procedure, this would suggest that at some point before March 2018 the UK will no longer be deemed eligible to act as rapporteur.

Following a meeting with industry stakeholders held earlier this month, the European Medicines Agency, which allots rapporteurships for new drug applications, said that rapporteurs are appointed in a way that allows "the use of the best and available expertise in the EU in the relevant scientific area. In the current context, 'available' is interpreted as being available also beyond 30th March 2019" (i.e., the day after the official Brexit date of March 29, 2019).

"As the average length of a centralised evaluation for initial MAAs is more than 1 year, it was noted that this is already starting to take effect with regards to UK rapporteur appointments for new medicines," the EMA commented in a report on the meeting.

A spokesman for the agency said: "EMA is working on the basis of the scenario that the UK withdraws from the EU by the end of March 2019 and becomes a third country. Notwithstanding the ongoing [Brexit] negotiations, this means that UK rapporteurs are still being appointed for those marketing authorisation applications that are expected to be finalised by the end of March 2019."

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Losing its rapporteurships will be a blow to the UK Medicines and Healthcare products Regulatory Agency, which has been a key player in the assessment of new EU centralized drug applications. Between January 2015 and December 2016, for example, the UK was chosen as rapporteur for 15% of products that came up for appointment, and was co-rapporteur in 13% of cases.

It was suggested earlier this year that the MHRA had asked the EMA not to stop appointing it as rapporteur in the run-up to Brexit, and that this could be enabled via a multi-year transitional arrangement after Brexit to allow more time to reallocate products where the UK had acted as rapporteur. *(Also see "Massive Reallocation of UK Rapporteurships Likely As EMA Plans For Future; UK's Interim Role Uncertain" - Pink Sheet, 11 May, 2017.)*

But with the slow pace of negotiations and growing uncertainty over whether the UK and the EU will manage to negotiate a Brexit deal in time, the EMA will need to proceed on the assumption that there will be no such arrangements.

The EMA stresses that the MHRA and UK experts are still engaged in other EMA activities "and will continue to do so until the UK withdraws from the EU," and that there is "regular high level communication with MHRA around Brexit preparedness activities."

REDISTRIBUTION OF WORK

In the meantime, the agency is working with the other 27 EU member states to ensure an "orderly redistribution" of the regulatory and scientific work that is currently done by the MHRA.

This includes the distribution of initial MAAs (including the reassignment of procedures that have not yet started but have been assigned to the UK), licenses for approved drugs for which the UK acted as rapporteur or co-rapporteur, scientific advice, procedures at the agency's Pharmacovigilance Risk Assessment Committee, inspections, and so on.

Action on these issues is being led by the EMA's working groups on operational preparedness (covering human and veterinary medicines), which are due to meet in November to discuss redistribution scenarios for legacy products and make some recommendations to be agreed by the network and the EMA management board in December.

"The changes are not expected to come into effect before Q3 2018 with adequate time foreseen for knowledge transfer," the report says. To facilitate product transfer, marketing authorization holders should play "an important role," for example in meeting with the new rapporteur's team.

The EMA also stresses the importance of transparency in communications: "It will be key for industry to keep EMA well informed of any foreseen changes to the timing of initial MAA submissions and to better share post-authorisation lifecycle submission planning," particularly for products with UK rapporteurs.

INDUSTRY CONCERNS RAISED

The industry viewpoint was put at the meeting by Alan Morrison of the European industry federation EFPIA and its European Biopharmaceutical Enterprises group, on behalf of the other industry bodies representing biotech, generic, vaccine and OTC drug companies.

A "hard-Brexit scenario" was "clearly not the preferred option" for industry, the report says, noting that concerns were voiced around business continuity and supply chain disruptions, with industry stakeholders saying an early decision on the future UK-EU relationship and a long transition period were needed to mitigate such issues and ensure the necessary changes, such as technology transfers, could be undertaken.

Companies would also have to make the necessary legal and regulatory arrangements for batch testing, certification and release of products, the meeting heard. In light of the high number of regulatory submissions that would need to be made in a short timeframe, together with the issues raised by the EMA's relocation, industry called for "simplification and flexibility" around timelines and administrative requirements "where at all possible."

Before the meeting, industry stakeholders had put together a list of detailed questions to highlight areas where more clarity is needed. As it was thought that the meeting was not the appropriate forum to discuss and feed back on these ideas, it was agreed to organize follow-up discussions on the following topics:

- Regulatory marketing authorization holder transfers: transfer versus variation, timelines etc.
- Manufacturing and supply chain: good manufacturing practice status, batch testing, acceptance of UK qualified person testing beyond March 30, 2019.
- Pharmacovigilance: changes relating to the qualified person for pharmacovigilance (QPPV), access etc.
- Cross-project activities such as telematics.

FUTURE PLANS

The next phase of the EMA's Brexit preparedness business continuity plan, which will be launched on Jan. 1, 2018, is currently under discussion and more information will be released after the December management board meeting. The first phase of the business continuity plan, which was released earlier this month, deals with all Brexit-related affecting the EMA, including its relocation from the UK to another member state; the new location is to be decided on Nov. 20.

In the meantime, an industry-wide survey across the trade associations is under way with a view to gathering insights into "short- and long-term company impact and timing of decision making." Depending on what emerges from this, the EMA may conduct its own survey to collect more detailed information on issues like supply and availability of products.

In addition, industry stakeholder meetings or webinars will be scheduled every two to three months to discuss Brexit-related matters, and regular procedural guidance and updates of the EMA's question and answer document will be released.

From the editors of Scrip Regulatory Affairs. Published online October 30, 2017

The BeNeLuxA Medicines Access Coalition: Resetting The Balance of Power in Europe?

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The BeNeLuxA coalition for improving access to medicines in Europe could signal a "resetting in the balance of power" between companies and government payers when negotiating drug prices, says the European Public Health Alliance. EPHA also suggests that countries could take their collaboration further by working together on new models of funding R&D.

The BeNeLuxA initiative is a collaboration between Belgium, the Netherlands, Luxembourg and Austria that focuses on four main areas of work: joint horizon scanning; joint Health Technology Assessments; information exchange; and joint price negotiations (but not joint procurement). The coalition looks set to expand and more pricing pilots are under way. *(Also see "Is Europe's BeNeLuxA Coalition Moving Too Fast?" - Pink Sheet, 14 Sep, 2017.) (Also see "New BeNeLuxA Access To Meds Initiative Pilots Are Under Way" - Pink Sheet, 1 Sep, 2017.)*.

In a reflection paper entitled "BeNeLuxA: First results of multi-country cooperation on medicine price negotiations", EPHA examines the outcome of a pilot that saw the Netherlands and Belgium negotiate with **Vertex Pharmaceuticals Inc.** over the price of its cystic fibrosis drug *Orkambi* (lumacaftor/ivacaftor). Both countries concluded that the drug was not worth what the firm was asking for, and that without a better offer from Vertex it would not be made available. *(Also see "Where Europe's 'BeNeLuxA' Joint Pricing Pilot May Have Gone Wrong" - Pink Sheet, 30 Jun, 2017.)*

INFORMATION ASYMMETRY

The paper points to the problem of "information asymmetry" between pharmaceutical companies and government payors. This, it says, is an approach to pricing talks "favored by the industry" that leads to higher prices and gives companies the upper hand.

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> "Payers and governments across Europe are empowered by the solid, public and evidence based rejection of Vertex's offer" – EPHA

When firms negotiate with one member state at a time, they gain a "panoramic view" of each of the 28 EU member states' pharmaceutical policies, purchasing power and willingness to pay, while national payers learn little about pricing in neighboring countries because of "market fragmentation and the shroud of secrecy that covers pharmaceutical decision-making," according to the position paper.

Companies are able to "game the system" by offering governments "tailored" agreements, while smaller and poorer countries lose out the most," it says. "The arrangement has been enabled by governments through national legislation which guarantees and consolidates this confidentiality through secrecy clauses and non-disclosure agreements. Presumably each government is assured that they are getting a preferential deal."

While all this might work to the advantage of a big country with the purchasing power of Germany or France, "smaller and poorer countries are most affected by this power imbalance," it adds.

But the talks between Vertex, Belgium and the Netherlands send a signal that the sands could be shifting. The pilot may not yet have led to an agreement in the case of Orkambi, but "there is reason for optimism that it will yield better results for patients and health systems in the near future," says the paper. "Payers and governments across Europe are empowered by the solid, public and evidence based rejection of Vertex's offer," it adds.

There are several lessons to be taken

from the pilot, says EPHA. For example, collaboration is possible, and responsibility is shared, when two or more member states succeed in working together and overcome their differences, such as language barriers, working methods and priorities. In addition, the Orkambi talks demonstrate the important role that HTA plays "as a gatekeeper for the system and as an enabler of genuine therapeutic advance." The Orkambi outcome "illustrates HTA's role as a tool to rationalize and not ration pharmaceutical expenditure," it says.

INDUSTRY PUSHBACK?

However, whether such cooperation will become "the new normal" for negotiating drug prices is unclear at this point, given that intergovernmental collaboration may still be susceptible to changes in local political landscapes.

Furthermore, EPHA notes that the pharmaceutical industry is cautious about initiatives such as BeNeLuxA and points to concern that "companies might attempt to slow down or 'boycott' these initiatives, so as not to set a new precedent." Governments "might wish to respond to any such actions by making the BeNeLuxA route the only available option for reimbursement of a company's products or for some clusters of products," it suggests.

The paper also proposes that government could go further in working together to explore alternative models of funding pharmaceutical R&D that are not centered around patent-based monopolies and exclusivities. The paper points to existing projects, for example, the Fair Medicine Initiative, the Drug Pricing Scenarios Project and the Fair Pricing Forum.

The question of new models of R&D funding was also raised at the European Health Forum Gastein, held in Austria last month, where speakers and delegates discussed issues such as the true value of innovation and the link between intellectual property protections and high drug prices. *(Also see "Trenches, Silos And Circular Debates: European Health Forum Calls For Collaboration On IP And Medicines Access" - Pink Sheet, 30 Oct, 2017.)*

Published online November 2, 2017

US FDA Recognizes Eight EU Authorities, Triggers Mutual Recognition Provisions

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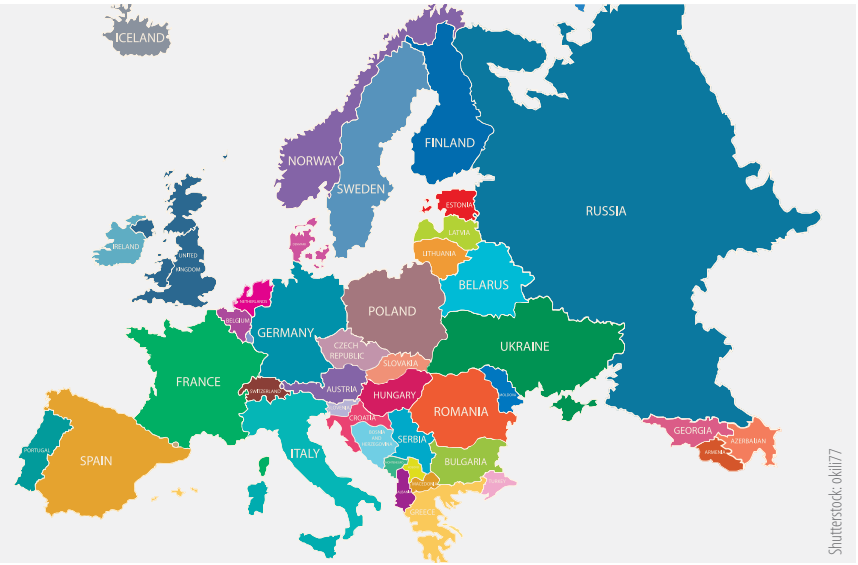

The US FDA has named the first eight European drug regulatory authorities that it is recognizing under a US/EU mutual recognition agreement reached in March.

It will now be the exception rather than the rule for FDA to inspect pharmaceutical manufacturing facilities in these countries: Austria, Croatia, France, Italy, Malta, Spain, Sweden and the UK.

FDA will henceforth determine compliance status based on domestic inspection findings of authorities in those countries. However, the determinations it makes based on those findings won't necessarily mirror the decisions of foreign authorities.

FDA's recognition of the eight countries on Oct. 31 meets a Nov. 1 deadline that triggers key provisions of the agreement, most notably the EU's recognition of FDA's domestic inspection findings. However, EU inspectorates already had begun to defer US inspections in anticipation that FDA would meet the deadline. *(Also see "EU To Defer US GMP Inspections Ahead Of Mutual Recognition Agreement Becoming Operational In November" - Pink Sheet, 27 Jun, 2017.)*

The EU had recognized FDA in June and added the agency to its list of recognized authorities on Aug. 11. A separate Aug. 23 agreement with the European Commission enabled FDA to share commercially confidential information with its European counterparts. No longer will the agency have to redact such information from inspection reports before sharing them with EU authorities. *(Also see "EU, US Commit To Sharing Full Inspection Reports To Supplement GMP Mutual Recognition" - Pink Sheet, 24 Aug, 2017.)*

FDA must recognize the other 20 EU member states by July 15, 2019, for the mutual recognition agreement to remain in effect.

The agreement will apply to each European country as FDA recognizes them. It is unclear when these recognitions will occur or to what extent they will be announced.

AGENCY LEADERS LAUD MILESTONE

Agency leaders on both sides of the Atlantic provided written statements lauding the latest development.

FDA Commissioner Scott Gottlieb emphasized the importance of the agreement in enabling the agency to focus more inspectional resources on higher-risk countries, while Guido Rasi, executive director of the European Medicines Agency, noted that this is the EU's sixth such agreement with third-country parties. Dara Corrigan, FDA's acting deputy commissioner for global regulatory operations and policy, and a chief architect of the agreement, called it an "unprecedented and significant step."

Ellen Morrison, assistant commissioner for medical products and tobacco operations in FDA's Office of Regulatory Affairs, Oct. 31 told the annual meeting of the International Society for Pharmaceutical Engineering in San Diego, California, "we are excited about this. The agreement will allow regulators to use inspection reports to help determine whether facilities are making high-quality drugs."

In response to a question, Morrison said FDA's addition of Germany to the agreement is "still under discussion." Corrigan and others have called attention to the complexity of evaluating Germany due to the provincial nature of its inspectorate. Morrison said, "we hope it's going to be this year."

KEY PROVISIONS TRIGGERED

Some aspects of the revised mutual recognition agreement took effect March 2, the day after its signing was completed. *(Also see "EU, US Finally Agree On Mutual Recognition Of GMP Inspections" - Pink Sheet, 2 Mar, 2017.)*

Other aspects took effect Nov. 1, when the agreement became operational, such as the cessation of routine inspections by EU authorities in the US and routine FDA inspections in the first eight EU countries the agency has recognized.

By meeting the Nov. 1 deadline, FDA triggered four key articles of the agreement, which was incorporated as an amended pharmaceutical sectoral annex to a 1998 mutual recognition agreement between the US and the EU. *(Also see "Why Now Is The Right Time For Mutual Recognition" - Pink Sheet, 3 Mar, 2017.)*

> FDA Commissioner Scott Gottlieb emphasized the importance of the agreement in enabling the agency to focus more inspectional resources on higher-risk countries, while Guido Rasi, EMA's executive director, noted that this is the EU's sixth such agreement with third-country parties.

These articles require the parties to accept each other's inspection findings, though with some exceptions, as well as share GMP documents, request inspections, and continue to assess each other.

ARTICLE 8: recognition of inspections. This article requires the parties to accept "official GMP documents" concerning domestic facilities of recognized authorities, which means relying on the document's factual findings.

However, there are exceptions. An authority can decline to accept GMP documents because an inspection report appears to have "material inconsistencies or inadequacies," or is overshadowed by evidence of quality defects or consumer safety issues arising from post-market surveillance or complaints.

The declining authority must explain why it won't accept the report and request clarification. The authority that produced the GMP documents must respond, typically based on input from members of its inspection team.

ARTICLE 10: transmission of official GMP documents. This article sets forth a process for sharing GMP documents. It gives an exporting country's authority 30 days to share such documents with the importing country, if requested. If the importing country determines, based on its review of the GMP documents, that a new inspection is in order, it can request one per Article 11.

ARTICLE 11: requests for pre-approval and post-approval inspections. This article sets forth a procedure for requesting pre-approval and post-approval inspections.

An authority that receives such a request gets 15 days to say whether it will do the inspection. Such requests would most likely arise in the context of an application for marketing approval or of information warranting for-cause inspections.

If the requested authority believes it has relevant GMP documents, it should alert the requesting authority and provide the documents upon request.

ARTICLE 12: maintenance. This article calls for regular audits or assessments of each authority to make sure it continues to merit recognition.

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

HHS Secretary Search: Alex Azar Checks The Most Important Box

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On Oct. 30, Ranking Democrats on the Senate HELP and Finance Committees Patty Murray and Ron Wyden, respectively, sent a letter to President Trump that included a list of 51 policies and ideas that any nominee for HHS Secretary would be "expected" to support.

Murray and Wyden vowed to "closely scrutinize" any nominee to replace Tom Price to ensure they "champion" a range of policies: protect and improve Medicare and Medicaid to supporting strong safety and efficacy standards for drugs and devices. Those are just a few examples.

But missing from the list was the most critical prerequisite for the next nominee for HHS: competency.

Managing HHS is akin to governing a very large state – with a budget of close to $80 billion, it resembles Florida – which is why the job has tilted toward governors in recent years. Of the last five confirmed HHS Secretaries, not including Tom Price, three were governors – Kathleen Sebelius, Michael Leavitt, and Tommy Thompson – and one had executive level experience, Sylvia Burwell.

Regardless of the choice, it would seem unlikely at this point for the Trump Administration to get a confirmed HHS Secretary before 2018.

The diversity of management functions is almost on par with a state: disaster relief, addressing the opioid epidemic, administration and oversight of Medicare and Medicaid, setting and enforcing insurance rules enacted through the Affordable Care Act, the Indian Health Service, setting research priorities through NIH, not to mention FDA and the regulation of food, drugs, devices, and tobacco products.

That why when news broke Oct. 17 in a *Politico*report that the administration was considering Alex Azar for the position, the sound you heard around Washington may have been a collective sigh of relief from those who understand the magnitude of the job.

Azar would bring extensive knowledge of the sprawling department as Congress attempts to pass legislation to stabilize the insurance exchanges.

From 2001-2005, Azar served as HHS General Counsel under Tommy Thompson in the George W. Bush Administration. He was elevated to Deputy Secretary under Michael Leavitt, who followed Thompson as Secretary.

Following his service at HHS, Azar was named President of Lilly USA – which included men's health, women's health, neuroscience, immunology, cardiology, and Alzheimer's sales teams, as well as U.S. marketing function and negotiations with health insurance plans. Annual US revenue for 2016, Azar's last year, was $3.2 bil. (up 14% compared to the prior year). All that to say that **Eli Lilly & Co.**'s US affiliate is a very large and complicated organization to manage.

The choice of Azar would put an expert on the legal and regulatory complexities of drug policy at the top of the department just as the administration is readying an executive order on drug pricing and engaging with manufacturers on novel outcomes-based contracting models.

Azar left Lilly at the beginning of 2017 with the change in executive leadership at the company and started his own consulting firm, Seraphim Strategies.

His position as a former pharmaceutical executive may be viewed as a political liability given drug pricing is among the top domestic policy issues.

To that end, the Congressional Progressive Caucus sent a letter to President Trump on October 26 advocating against Azar as the choice for that reason. "Mr. Azar's appointment would send a very clear signal that your Administration is happy to put the pharmaceutical fox in charge of the health care henhouse."

The Murray/Wyden letter may be viewed as a more muted response in that context – and potentially more receptive to the nomination of Azar.

Moreover, it could be easily argued the that Trump Administration official with the closest ties to the drug industry, Scott Gottlieb, has delivered a superior performance of his job compared to his peers due in part to his knowledge of the complexities of the issues.

Azar would come from that same starting position except with deeper and more direct experience in the department.

There have been rumblings that current Department of Veterans Affairs Secretary David Shulkin could emerge as the choice. However, Shulkin may be painted with the same jet setting brush as Price making him an unnecessary risk for the administration. Plus, the administration would have to find a replacement for Shulkin if there was a switch.

Regardless of the choice, it would seem unlikely at this point for the Trump Administration to get a confirmed HHS Secretary before 2018.

Should Trump bypass Azar and Shulkin, New Jersey Governor Chris Christie may sit near the top of any short list for the position

given his experience as CEO of a state and his status as one of President Trump's earliest supporters.

Christie has effectively managed the President's Commission on Combating Drug Addiction and the Opioid Crisis and the related high-profile issues. The final report was delivered Nov. 1.

Also playing is Christie's favor is the one individual who has publicly acknowledged blocking Christie from consideration for any cabinet-level job, White House Chief Strategist Steve Bannon, is gone.

There are a number of external candidates outside of Azar who could be vetted for the position.

Mark McClellan may stand above them as one outsider with strong qualifications and support for the HHS job. He is also a known quantity with a good reputation among both Republican and Democratic legislators based on his prior experience as head of both FDA and CMS.

He has managed his post-government career in a way that would allow him to re-enter government at a cabinet-level or high profile White House position.

McClellan's think-tank work following enactment of the Affordable Care Act at the Brookings Institution Engelberg Center for Health Reform helped to moderate his perception in the eyes of Democrats after his service to the George W. Bush Administration.

McClellan's move to the Duke Margolis Center for Health Policy has solidified his stature as a health policy thought leader who stands above partisan politics. The center's work on value-based outcomes contracting and real-world evidence puts McClellan at the forefront of key health policy areas being debated in Washington. His nomination would likely be welcomed by both sides.

All that said, it appears that Azar is the favorite at this point and the President may be edging closer to making the choice official. One advisor to the President went as far as to say Trump himself had signed off on the pick, according to *Politico*. If so, Azar would bring welcome stability and competency to the department.

From the editors of the RPM Report. Published online November 1, 2017

FDA's NDA And BLA Approvals: Varubi, Prexxartan, Calquence

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				
Tesaro	*Varubi* (rolapitant)	Injectable emulsion to be used in combination with other antiemetic agents in adults to prevent delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.	S, 3	10/25/2017
Carmel Bioscience	*Prexxartan* (valsartan)	Oral solution to treat hypertension in adults and children six years and older, to lower blood pressure; to treat heart failure (NYHA class II-IV) to reduce the risk of hospitalization for heart failure in patients who are unable to swallow valsartan tablets; or to reduce risk of cardiovascular death in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction who are unable to swallow valsartan tablets.	S, 3	10/30/2017
Acerta (AstraZeneca)	*Calquence* (acalabrutinib)	Treatment of adults with mantle cell lymphoma (MCL) who have received at least one prior therapy.	P, 1	10/31/2017

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

Biosimilar Global Reference Standard Intrigues US FDA, But Many Questions Still To Answer

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US and European regulators may like the idea of creating a global reference standard for biosimilars, but believe legal and other issues associated with it likely mean the idea is years away from being implemented.

A global reference standard would set one approved version of an innovator product as the basis for a biosimilar's development. The intent is to eliminate the need to mandate bridging studies showing the domestic- and foreign-licensed products are the same to allow comparison to the proposed biosimilar.

The US FDA did not dismiss the concept in theory, but said in practice there were several issues that would have to be resolved before it could be implemented.

Leah Christl, associate director for therapeutic biologics in FDA's Office of New Drugs, said Oct. 25 during the DIA Biosimilars Conference that the agency has many concerns, but that doesn't mean the idea does not have merit.

"Right now there's a lot of assumptions that would go into that kind of an approach, and I think … there's a lot of validation that would have to be done around that," she said. "There's some very large questions that would need to be answered first, but it's not to say that we shouldn't start to tackle the scientific issues sooner rather than later."

Leon Van Aerts, senior assessor at the Netherlands' Medicines Evaluation Board, echoed that there are unknowns preventing such a move now, but in the coming years, it could be possible.

"As we are still learning I think at this moment, it might be a little too early to make such a major step," he said. "If we learn more and have more insight in the relationship between both attributes and clinical outcome, maybe we could at a certain point, we can make such a decision."

Christopher Webster of BioApprovals and Gillian Woollett of Avalere proposed the global reference standard idea in an article for the journal BioDrugs. They argued analytical and clinical pharmacokinetic bridging studies between domestic and foreign versions of the same biologic reference should be eliminated because they are unnecessary, redundant, and costly.

In the paper, Webster and Woollett offered three criteria for a global standard: that the reference biologic be approved in a jurisdiction that has adopted ICH comparability standards, that global reference and the locally-licensed reference share the same form, route of administration, API content and excipient composition, and that there be substantial public evidence the reference and locally-licensed biologics have been approved based on essentially the same original data.

The Association for Accessible Medicines and its Biosimilars Council supported the idea, but the Biotechnology Innovation Organization did not. *(Also see "Biosimilars: Adoption Of Global Reference Comparator Would Eliminate Bridging Studies" - Pink Sheet, 7 Aug, 2017.)*

LEGAL HURDLES AN FDA CONCERN, TOO

Product divergence seemed to be an immediate concern for the FDA and EU officials.

Van Aerts said the same product could be manufactured at different sites and be different from each other. He said it is unclear whether those differences matter.

"We are still … in the learning curve of what these small differences actually mean," he said. "We do not know exactly how much deviation would be needed in order to have a clinical significant difference."

Christl made a similar argument, saying that products still can diverge even with they are approved based on the same clinical studies, in part because manufacturing changes are not always made at the same time globally.

"We have reference products that may have been approved in different jurisdictions based on the same clinical package, but after that there is a life-cycle management aspect of it," she added.

Christl also said that there are legal issues that also would have to be resolved, such as confidentiality, to implement a

global standard.

"It's not to say that we shouldn't try to tackle those challenges … there would be a lot to do," she said. "Right now it's not a quick answer or something that could be quickly implemented by any stretch of the imagination."

OPPORTUNITY TO STREAMLINE DEVELOPMENT

Sponsors are excited about the global reference standard idea in part because of its potential to cut development time and cost. In many respects, a single reference standard would be the culmination of industry's desire to have regulators harmonize biosimilar development requirements to help speed approvals.

Beyond any potential harmonization efficiencies, FDA is encouraging sponsors to use the product development meeting system to talk about CMC and other issues, in addition to analytical similarity, in part to speed review and approval.

A streamlined development process could help lower the products' cost for patients and increase access. FDA Commissioner Scott Gottlieb has included biosimilars as part of his agency effort to help lower drug prices for patients. *(Also see "Biosimilars: US FDA Education Campaign Is Non-Committal On Non-Medical Switching" - Pink Sheet, 24 Oct, 2017.)*

Published online October 29, 2017

Generic User Fee Transition A Little Bumpy For Contract Manufacturers

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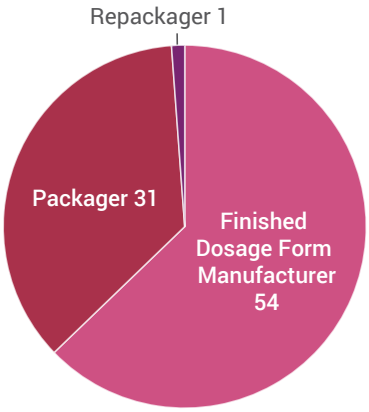
Contract manufacturers apparently did not join the US FDA generic drug user fee program's facility self-identification process as smoothly as intended, due in part to unfortunate timing of the legislative renewal of the program that prevented guidance development.

FDA asks generic drug manufacturers to voluntarily report their facilities and associated functions each year to help the agency keep an updated list of where products are made for the US market.

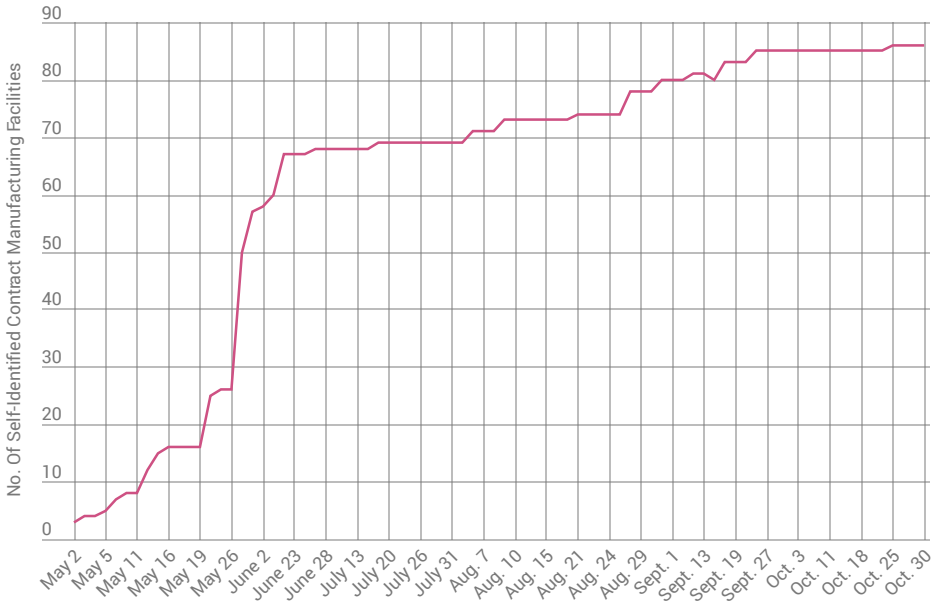
As part of GDUFA II, the new iteration of the Generic Drug User Fee Act, contract manufacturers were added as a category in the facility database, but the timing of the self-identification period for fee-setting purposes and reauthorization of the user fee program apparently prevented some CMOs from participating, according to minutes of an FDA-industry meeting on

Types of Self-Identified CMO Facilities



Note: *Data as of Oct. 30.*
Source: FDA

CMOs Registered With FDA From The Beginning



Not surprisingly, the majority of contract manufacturers that have self-identified with FDA under the generic drug user fee program for FY 2018 were finished dosage form manufacturers. But even though there were questions about the availability of the CMO self-identification option when the process began in May, many CMOs still registered. Most self-identified before GDUFA II became law in August.

GDUFA II implementation released Oct. 30.

During the Sept. 21 session, industry representatives said the CMO option for self-identification was not available in May when the fiscal year 2018 process opened.

Gil Roth, president of the Pharma and Biopharma Outsourcing Association, which represented CMOs during GDUFA II negotiations, told the Pink Sheet that "there were unavoidable issues centering around the timing of [the FDA Reauthorization Act's] passage, the self-ID period necessary for setting FY 18's fees, and the need to educate facility owners about the new fee model, and that meant some CMOs weren't able to self-ID their sites as CMOs for fee-setting purposes because they weren't using FDA's self-ID web-portal."

FDA said in the minutes that because GDUFA II was not reauthorized until August, when FDARA (which included the GDUFA reauthorization) was signed by President Trump, it "did not have the legal authority to include this option," but said now all self-identification options are available.

FDA told the Pink Sheet that the option to self-identify as a CMO was available in the Center for Drug Evaluation and Research's web portal when the self-ID process began, but "the agency however, could not officially publish technical guidance because GDUFA II was not enacted."

"Individuals who sought guidance prior to the FY 2018 open period were able to successfully submit their self-ID [structured product labeling] files," the agency told the Pink Sheet.

The CMO count is important because they pay only one-third the annual facility user fee under GDUFA II. *(Also see "GDUFA II: ANDAs, Not Facilities Will Govern Revenue" - Pink Sheet, 26 Sep, 2016.)*

The CMO count is important because they pay only one-third the annual facility user fee under GDUFA II.

Roth said the number used to calculate the CMO fee was acceptable despite the problems. "We're confident in the CMO and non-CMO finished dosage form count used to generate this year's facility fees, and believe that future years of GDUFA II will iteratively refine those figures," he said.

In FY 2018, domestic CMOs will pay $70,362, while domestic finished dosage form facilities will pay $211,087. *(Also see "Generic User Fee Hikes Could Disrupt US FDA Drug Pricing Campaign" - Pink Sheet, 28 Aug, 2017.)*

FDA will rely on self-ID data to find CMOs more than other manufacturers because contract facilities are not easily identified in approved applications, the agency said in the minutes.

Even though the voluntary self-identification process remained for GDUFA II, the agency changed its primary source for facility data. FDA now is using ANDA and other application data to determine its facility counts for user fee calculations. *(Also see "US FDA Changes Data Source For GDUFA II Facility Fee Setting" - Pink Sheet, 29 Aug, 2017.)*

DATA SHOWS CMOS REGISTERED WITH FDA EARLY IN PROCESS

FDA's facility self-identification data files, which are updated nearly daily, have included facilities labeled as contract manufacturers since at least May 2, the second day of the FY 2018 self-identification period.

That day there were only three facilities that said they were contract manufacturers, but by June 1, when the self-identification period closed, there were 57. On Aug. 17, one day before FDARA was signed, making the option legally available, there were 73 contract manufacturing facilities self-identified.

As of Oct. 30, there were 86 contact manufacturing facilities listed in the self-identification database. (*See charts, p. 13*).

The majority of self-identified CMOs (more than 62%) were classified as finished dosage form facilities. Another 36% were packaging facilities. One additional CMO said it was a repackager.

FDA said in the meeting minutes that the CMO identification process went "smoothly," and that it already was receiving fee payments.

The agency will depend on application filings for most of its user fee revenue in GDUFA II. In GDUFA I, most of the funds came from facility fees. *(Also see "GDUFA II: ANDAs, Not Facilities Will Govern Revenue" - Pink Sheet, 26 Sep, 2016.)*

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Questions Surround Merck's Withdrawal Of Keytruda Filing For Lung Cancer In EU

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Merck & Co. Inc.'s decision to pull its PD-1 inhibitor *Keytruda* (pembrolizumab) from the EU approval process for lung cancer has raised a few eyebrows, with some analysts saying the company was jumping the gun in seeking marketing authorization on the back of Phase II trial data. It will now have to wait until Phase III results are ready before filing again.

At least one analyst says he may have to revise his forecast for Keytruda sales growth, which was based partly on the expected EU approval of the drug in non-small cell lung cancer (NSCLC) in combination with chemotherapy.

Merck announced on Oct. 27 that it had withdrawn the EU marketing authorization application for the use of Keytruda in combination with pemetrexed and carboplatin for the first-line treatment of non-squamous NSCLC. The application to the European Medicines Agency had been based on results from cohort G of the of the Phase II KEYNOTE-021 study, which formed the basis of the product's US approval for this indication in May. *(Also see "Keytruda/Chemo Combo Approval Means Merck Holds Crown, For Now" - Pink Sheet, 10 May, 2017.)*

Commenting on the withdrawal, the firm said only that it was confident in the clinical data from the trial, which it said showed "significant" improvements in the overall response rate [ORR] and progression-free survival [PFS] for the Keytruda combination compared with chemotherapy alone, and that it "looked forward" to sharing data from a number of other studies with the regulatory authorities "as they become available."

Possible problems with the indication were hinted at earlier this month when Merck appeared before the EMA's scientific committee, the CHMP, to answer questions on its NSCLC filing, having failed to secure a recommendation for this use at the committee's September meeting. *(Also see "Roche Fails Again To Convince CHMP On Ocrevus, Only Teva Gets A Thumbs Up" - Pink Sheet, 13 Oct, 2017.)*

But the exact reasons for the withdrawal are not clear. Datamonitor Healthcare analyst Dustin Phan said that Merck's decision to make overall survival (OS) a co-primary endpoint (with progression-free survival) in the confirmatory KEYNOTE-189 study "was already rather surprising, given that its readout would be delayed by 18 months, long after **Bristol-Myers Squibb Co.**'s CheckMate-227 [with Opdivo/Yervoy] produces results." *(Also see "Merck Stresses Overall Survival In Keytruda/Chemo '189 Trial Revamp" - Pink Sheet, 27 Oct, 2017.)*

Phan suggested that the withdrawal of the EU application, together with the changes to KEYNOTE-189, "together appear to suggest that Merck is trying to ensure that Keytruda confers a survival benefit over standard therapies."

PD-1/PD-L1-targeted immunotherapies have on several occasions failed to demonstrate significant or meaningful improvements in PFS while ultimately conferring survival advantages over chemotherapy, Phan noted.

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> The withdrawal "could be a strategy by Merck to ensure regulatory as well as commercial success"
> – Datamonitor Healthcare analyst Dustin Phan

"In addition, physicians and patients are placing increased emphasis on overall survival, as are regulatory bodies like the EMA and [the US] FDA. As a result, this could be a strategy by Merck to ensure regulatory as well as commercial success," Phan observed. Notably, the first-line Phase III trials for all three leading immunotherapies – KEYNOTE-189, CheckMate-227 and IMpower-150 (with Roche's Tecentriq) – now have OS and PFS as co-primary endpoints, he said.

TIMING OF THE ANNOUNCEMENT

The timing of Merck's announcement also attracted some attention. Sanford Bernstein analyst Tim Anderson said the company had decided not to disclose the news during its Oct. 27 third-quarter earnings call because it intended to wait until the CHMP made its announcement around mid-November.

However, because the company was questioned about the KEYNOTE-021 study in Europe on the Oct. 27 conference call, "it felt compelled to disclose this news now.Admittedly this is an awkward development."

It is now clear, Anderson said, that the "CHMP's approval was likely only going to happen once the Phase 3 KN-189 trial reported out. And, since the read-out of that trial is now delayed because of an endpoint change (at least on OS; new guidance is early 2019 vs

It is not clear why Merck filed Keytruda at the Phase II data stage. Evercore analyst Umer Raffat suggested that the company "attempted this filing as a long shot, while knowing there is not a clear path for approval" in the EU based on Phase II studies."

1H-2018 before), the KN-021G application was not going to be approved anytime soon, leading to its withdrawal."

This development "may cause us to revisit our EU Keytruda forecasts," said Anderson, who had expected the NSCLC approval in 2018. "In 2017 we forecast international sales of $1,556m growing to $2,513m in 2018." EU approval in first-line lung cancer in combination chemotherapy "is part of this growth."

TIMING OF THE FILING

It is not clear why Merck filed Keytruda at the Phase II data stage. Evercore analyst Umer Raffat suggested that the company "attempted this filing as a long shot, while knowing there is not a clear path for approval" in the EU based on Phase II studies. "However, Merck may have thought that given the magnitude of response and OS data, perhaps EMA may consider it."

He noted, though, that the EMA had approved Keytruda in untreated urothelial carcinoma based on results of a single-arm Phase II study (KN-052), and wondered why the agency did not do the same for lung cancer. Merck's response, he said, was that NSCLC was a "much broader indication and that may have played a role here."

Having looked further into the data, Raffat said, he noticed that the EMA had actually called KN-052 data in urothelial carcinoma "not that compelling". The EMA had commented: "Taking into account the historical data in the target population, observed ORR data are not that compelling, even in the PD-L1 strongly positive cohort. Data on the median duration of response compare favourably, but are still immature. The same applies for time to event endpoints PFS and OS. Moreover the duration of follow-up is still insufficient."

He noted that the CHMP first made a request for additional data in June 2017 "(i.e., well before there could have been a possible interim on KN-189)", but that "to be clear, it seems that CHMP made a second request for supplementary information with a specific timetable as of 14 September."

Bernstein's Anderson said that earlier in 2017 he had been "surprised to learn that the EU application had been accepted for review in the first place – we can now infer that '189 results were needed for a positive ruling, but because of the new delay in their release, the application was doomed. These are the sort of regulatory nuances that sometimes become clear only after the fact – Merck had not made it known previously that '189 was a necessary part of the review process, but it should have been obvious."

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China Cuts Drug Approval Timelines, Sets Tough Penalties On Individuals Violating R&D Or Safety Rules

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The China FDA on Oct.23 released two draft amendments to current pharma regulations for public comments - one an amendment to the Drug Administration Law (DAL) and the other to the Drug Registration Regulation (DRR). DAL is a general law regulating pharmaceutical products in China while DRR provides more technical details for product registration.

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Both the drafts, long-awaited by industry, have been revised to reduce the current clinical trial and new drug review and approval timelines. The DAL draft, for one, allows study sponsors to initiate their clinical trials if no rejection or deficiency notice is received from the China FDA within 60 work days. The current timeline is 90 work days.

The DRR draft specifies the timeline for a new drug approval (NDA) to be 100 work days, a 33% reduction from the current 150 work days. For generics, biosimilars and traditional Chinese medicines the revised timeline is 120 work days.

Other key details of the DAL draft include:

- The nationwide rollout of a marketing authorization holder (MAH) mechanism. MAH holders will be responsible for pre-clinical, clinical, manufacturing as well as post-marketing studies and adverse events reporting. Foreign MAHs need to designate a domestic representative and both the domestic and foreign MAHs will share the liabilities;
- Elimination of the clinical site certification process; qualified clinical sites can conduct trials via a filing system;
- Consolidation of active ingredients and excipients approvals into the drug product's NDA process and;
- Streamlining GMP (Good Manufacturing Practice) and GSP [Good Storage Practice] verification via for-cause inspections, rather than a separate certification process.

Notable details of the DRR draft include:

- Foreign data are allowed towards a new drug registration in China. Foreign firms can start multi-center studies in China from Phase I, with mandatory pre-submission consultation with the CFDA's Center for Drug Evaluation(CDE);
- Sponsors should file annual progress reports of the clinical studies, and file timely reports if any major adverse events occur; and
- Clinical data protection is being provided for innovative new drugs, treatment for rare diseases and pediatric conditions. However, details will be released separately.

"These amendments, once implemented, will provide a more innovation-conducive environment for pharmaceutical companies, and will also be more aligned with international regulatory practices," Katherine Wang, partner at law firm Ropes & Gray, said in a Oct.26 note to clients.

The DAL draft, which was open for public comments for just one week until Oct.31, indicates the CFDA's intent to push through the revised law to the next legislative body and signals that the revisions already reflect rounds of discussions with the industry, Wang told Pink Sheet in an interview.

The DDR draft is open for public comments until Nov. 25.

TOUGH INDIVIDUAL PUNISHMENT

As CFDA shifts its regulatory scrutiny from granting certifications to conducting for-course inspections, the agency has proposed harsher penalties for individual violators; previously the emphasis was squarely on employers.

Per the DAL draft, individuals who are found to be directly responsible for clinical data forgeries and revocations of licenses will face a 10-year ban from working in the industry. And, those who are indicted and sentenced for drug safety violations are barred for life from getting involved in drug manufacturing, research and development, distribution and import and export.

Furthermore, if MAH holders and heads or executives who hold direct responsibilities at research institutes, drug manufacturers pharma wholesalers and healthcare facilities are found to have violated the laws or cause severe damage to society, they face a fine of 30-100% of their annual income earned from their employers.

"Unlike previously when the focus was placed on work units, the new proposal would levy a heavy punishment to individuals," noted Wang.

From the editors of PharmAsia News.
Published online November 1, 2017

Observational Studies Should Get Safe Harbor For Preregistering Protocols – Humana

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ISPOR/ISPE Recommendations On Good Practices For Studies Using Real-World Data

1. Determine whether study is a hypothesis evaluation treatment effectiveness (HETE) study or an exploratory study.
2. Post HETE study protocols on a public study registration site prior to conducting the study.
3. Publish HETE study results with attestation to conformance and/or deviation from the original analysis plan.
4. Enable opportunities for replication of HETE studies by other researcher using the same data set and analytic approach, whenever feasible.
5. Perform HETE studies on a different data source and population than the one used to generate the hypotheses to be tested, unless it is not feasible.
6. Authors of original study should work to publicly address methodological criticisms of their study once published.
7. Include key stakeholders including patients, clinicians, HTA/payers, regulators and manufacturers in designing, conducting and disseminating the research.

Drug treatment studies based on observational data should be able to benefit from the US FDA's proposed safe harbor for communications to payers if manufacturers publicly register their protocols ahead of time, **Humana Inc.** Chief Pharmacy Officer Laura Happe suggested.

Happe's remarks came at a conference on standards for real world evidence sponsored by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE) focused on joint recommendations on good procedural practices for treatment and comparative effectiveness evidence derived from real world data. (*See box.*)

Registration and other steps to make observational studies more rigorous could increase payor confidence in real world data. And adhering to the group's recommendations could benefit sponsors in other ways as well, Happe suggested.

Stakeholders should view the ISPOR/ISPE recommendations around registering observational studies as in line with FDA's draft standards on what constitutes "competent and reliable scientific evidence" to support health care economic information under Sec. 114 of the FDA Modernization Act, Happe proposed during the meeting, held in Washington, D.C. Oct. 20.

If FDA "is willing to use these recommendations, why not say 'OK, if we register our observational studies maybe we could all agree that might help meet that standard of competent and reliable information,'" she said. "And that would help when manufacturers are trying to decide what is covered by Sec. 114."

"We believe that comparative effectiveness and cost effectiveness are inextricably linked. When we improve health outcomes, we reduce cost." – Humana's Chief Pharmacy Officer Laura Happe

Sec. 114 allows manufacturers, under certain conditions, to provide health care economic information not in labeling to formulary decision-makers. Although the ISPOR/ISPE recommendation do not specifically address cost analyses, payers see that as an important aspect of comparative studies based on real world data, Happe pointed out. "We believe that comparative effectiveness and cost effectiveness are inextricably linked. When we improve health outcomes, we reduce cost."

FDA's draft guidance on Sec. 114, released in January, specifically mentions ISPOR standards as a way of ensuring evidence meets the threshold for "competent and reliable scientific evidence." *(Also see "Industry Communications With Payors: US FDA Okays Info On Investigational Drugs" - Pink Sheet, 19 Jan, 2017.)*

It says that in "evaluating whether the amount and type of evidence that forms the basis for a particular communication of [health care economic information] meets the generally-accepted scientific standards for such information, FDA will consider the

FDA representatives at the meeting did not specifically address the recommendation on registration. But one pointed out there are "overlaps" between the report's recommendations and a 2013 FDA guidance on pharmacoepidemiology safety studies using electronic health care data.

merits of existing current good research practices for substantiation developed by authoritative bodies (e.g., International Society for Pharmacoeconomic and Outcomes Research (ISPOR) or Patient-Centered Outcomes Research Institute)."

FDA representatives who attended at the meeting did not specifically address the recommendation on registration. But Robert Ball, who is with the Center for Drug Evaluation and Research, pointed out there are "overlaps" between the report's recommendations and a 2013 FDA guidance on pharmacoepidemiology safety studies using electronic health care data. Ball is deputy director of CDER's Office of Surveillance and Epidemiology.

FDA's guidance also reflects the "need for a protocol prior to the start of the study," Ball pointed out. *(Also see "Electronic Healthcare Data Can Be Used With Caution In Observational Safety Studies, FDA Says" - Pink Sheet, 10 Jun, 2013.)* The agency "requires those protocols to be submitted to the FDA for evaluation so it's not the same level of [public] transparency," he acknowledged. "But there is a review that is required."

CDER Office of Medical Policy Director Jacqueline Corrigan-Curay also attended the meeting and discussed FDA activities related to exploring the utility of real world evidence, including a number of demonstration projects. *(Also see "Real World Evidence Benefits, Limits Explored In US FDA Demonstrations" - Pink Sheet, 29 Oct, 2017.)*

MAKING OBSERVATIONAL DATA MORE RIGOROUS

The ISPOR/ISPE recommendations were published in September in the journal Value in Health. ISPE also published a companion set of recommendations on improving the reproducibility of health care database studies.

"To date, lack of confidence in observational research [e.g., real world data studies] has slowed the uptake of [real world evidence] into policy and many of the concerns have focused on methodological issues," it says. "Threats to the validity" of real world data studies on the effects of interventions include "unmeasured confounding, measurement error, missing data, model misspecification, selection bias and fraud."

The ISPOR/ISPE task force "strongly" encourages manufacturers to register studies in advance to foster transparency. "The posting of a study protocol and analysis plan on a public registration site provides researchers with the opportunity to publicly disclose the 'intent' of the study – exploratory or hypothesis evaluation – as well as the basic information about the study," the task force states.

Furthermore, "registration in advance of beginning a study is a key step in reducing publication bias because it allows systematic reviewers to assemble a more complete body of evidence by including studies that were partially completed or were inconclusive and therefore less likely to be published in a journal," the group explains.

Registration information could be posted to Clinicaltrials.gov, the EU Post-Authorisation Study Register or the National Library of Medicine's HSRProj for health services research, the task force suggests.

Clinicaltrials.gov may need to modified to make posting information on observational studies easier, the group notes. The site was designed for randomized clinical trials and although some observational studies have also been recorded there, "the process is not an easy one."

A FOCUS ON 'HYPOTHESIS EVALUATING' STUDIES

The recommendations focus on what the task force describes as "hypothesis evaluating treatment effectiveness (HETE) studies, which "evaluate the presence or absence of a pre-specified effect and/or its magnitude."

When evaluated in conjunction with other evidence, "the results may lead to treatment recommendations by providing insights into, for example, whether a treatment effect observed in [randomized clinical trials] gives the same result in the real world where low adherence and other factors" such as patient selection could alter treatment impact, the paper explains.

Other types of real world studies, described as "exploratory treatment effectiveness" studies, "primarily serve as a first step to learn about possible treatment effectiveness," are less pre-planned and allow for "process adjustments as investigators gain knowledge of the data," the paper explains.

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Trade Panel Bolsters FDA's View In Amarin Omega-3 Complaint

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The International Trade Commission agrees it's FDA's job to regulate the dietary supplement industry as it rejects **Amarin Corp. PLC**'s fair trade complaint alleging some omega-3 ingredients are unapproved new drugs.

The attempt by Amarin to eliminate competition for its Rx drug *Vascepa* from some omega-3 dietary supplements likely now won't be copied by other pharma firms that face competition in the marketplace from dietary supplements that contain ingredients similar to the active ingredients in their drugs. Vascepa contains the active ingredient icosapent ethyl – a synthetically produced ethyl ester approved as a drug to reduce triglyceride levels in adults with severe hypertriglyceridemia.

ITC, a Department of Commerce agency, on Oct. 30 published its decision not to investigate the complaint Amarin submitted Aug. 30 contending that dietary supplements containing purified eicosapentaenoic acid (EPA) or omega-3 formulations containing primarily EPA in ethyl ester or re-esterified form are actually drugs and asking the commission to block import of those ingredients by a number of companies. Had ITC investigated the complaint, found for Amarin and ordered a halt to the imports, the firm could have used that development as a step toward eventually seeking to prevent US marketing of all supplements containing those ingredients. *(Also see "Fair Trade Is Not FDA's Expertise, Amarin Says In Omega-3 Ingredients Filing" - Pink Sheet, 19 Oct, 2017.)*

"Amarin's complaint does not allege an unfair method of competition or an unfair act" as identified in ITC regulations, states the ITC decision made on Oct. 27.

Additionally, the commission said Amarin's allegations that some makers of certain omega-3 supplements of are committing advertising violations by "are precluded" by the Food, Drug and Cosmetic Act and "that the Food and Drug Administration is charged with the administration of the FDCA."

Shutterstock: Kraevski Vitaly

FDA made those arguments in an Oct. 6 letter to ITC recommending against investigating the firm's complaint. *(Also see "FDA Objects To Amarin Trade Complaint Against Omega-3 Ingredients" - Pink Sheet, 11 Oct, 2017.)*

ITC PATHWAY A DEAD END

Dublin-based Amarin's fair trade complaint to ITC was a novel strategy for challenging the regulatory status of dietary ingredients.

"It's not a typical ITC case," said Adam Ismail, president of the Global Organization for EPA and DHA (docosahexaenoic acid) Omega-3's.

It's also not likely to be emulated. "I don't think we're going to see a lot of movement in that direction," Ismail said in an interview.

Council for Responsible Nutrition President and CEO Steve Mister said that with the decision, ITC indicated "it is not going to let itself be used as a side track around FDA."

"I think this absolutely should send a signal to other pharmaceutical companies that might be thinking about doing this," Mister said.

Still, it's likely that if other pharma firms, like Amarin, receive FDA approval to market drugs developed from synthetics of nutritional substances with indications as treatments for diseases or health conditions, they could see dietary supplements containing similar nutritionals as competition.

"As the nutrition research gets better and better and we learn more about these ingredients, we are going to see more pharmaceuticals [with synthetic nutrients] that have disease treatment claims around them," Mister said.

After investing in clinical trials and other research to support new drug applications that gain FDA approval, pharma firms are entitled to market as drugs products containing synthetics of nutritionals as their active ingredients, he added.

But supplement firms also are entitled to continue marketing their products with other forms of the same nutritionals. "The difference being different claims for the dietary supplements," Mister said.

Should another firm consider a complaint similar to Amarin's, ITC's decision and FDA's letter to the commission point to the correct regulatory pathway, he added. "There is a process and FDA is the appropriate arbiter."

FIRST LITIGATION SETBACK FOR VASCEPA

A representative for Amarin said the firm would not comment on the ITC decision and on whether it would submit a citizen petition to FDA about the regulatory status of certain omega-3 ingredients. While its ITC request was denied, Amarin has prevailed in other litigation to improve Vascepa's chances in the market.

In 2015 it challenged FDA's agency's regulations on off-label drug promotion and seeking a determination that it could communicate to physicians information from studies on Vascepa's use by adults on statin therapy for high triglyceride levels.

A federal judge said truthful and non-misleading speech about the unapproved use of Vascepa in patients with persistently high triglycerides is not the basis of a misbranding lawsuit. The firm and FDA settled the litigation in an agreement that included an optional preclearance process for the company's future communications about off-label use of Vascepa. *(Also see "Off-Label Unleashed? Amarin Win Suggests Firms Still Need Strong Data To Skirt FDA" - Pink Sheet, 7 Aug, 2015.)*

Also in 2015, a federal court spotlighted FDA's apparently inconsistent definitions of what constitutes an "active ingredient" in rejecting the agency's rationale in 2012 for denying Amarin market exclusivity for Vascepa as a new chemical entity. The court ordered FDA to reconsider and the agency granted the exclusivity. *(Also see "Legal Briefs: Courts On Exclusivity; Namenda 'Hard Switch' Deemed Coercive; Acorda Fights Bass Patent Petition" - Pink Sheet, 1 Jun, 2015.)*

Most recently, in January 2016 a federal court granted Amarin's motion to dismiss paragraph IV patent infringement litigation with several companies that had submitted abbreviated ANDAs to FDA seeking approval to market generic versions of Vascepa.

From the editors of the Tan Sheet.
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EU-Mercosur Trade Deal Could See Brazilian Drug Spending Soar

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The next round of talks on a potential free trade deal between the European Union and the Mercosur countries in Latin America is set to run from Nov. 6-10 in the Brazilian capital Brasilia. Among the topics likely to be discussed are intellectual property rights, with critics claiming that EU proposals would introduce "TRIPS-plus" measures that would delay generic entry and cause Brazil to spend billions more on medicines.

The EU is negotiating the free trade deal with the four founding members of Mercosur – Argentina, Brazil, Paraguay and Uruguay. Talks began back in 2000 but have proved contentious and have stopped and restarted several times. Among the controversial issues are EU proposals that would extend obligations in the Mercosur markets to introduce data exclusivity and extend patent terms.

As talks have again gathered pace, proposals published by the EU last year are coming under scrutiny. A study published at the end of September by the Sergio Arouca National School of Public Health, Oswaldo Cruz Foundation (ENSP/Fiocruz), simulates what Brazil's healthcare system would spend on HIV/AIDS and hepatitis C treatments if the EU's proposals on intellectual property rights were accepted. It concludes that Brazil would spend an extra R$1.9bn ($581.4m) a year on these drugs alone.

The study looked at antiretrovirals bought in 2015 to treat HIV/AIDS, a market that the authors claim has been relatively stable in terms of government expenditure over recent years thanks to a large market penetration of generic medicines.

It also looked at the hepatitis C medicines purchased in 2016, including sofosbuvir (Gilead's Sovaldi) and daclatasvir (Bristol-Myers Squibb's Daklinza). The study points out that the hepatitis C market has grown sharply and is composed of medicines that are still under IP protection. According to the study, spending on these products would increase by R$1.8bn a year, while spending on antiretrovirals would go up by R$142 million, under the EU proposals.

"This is just the tip of the iceberg as the research is restricted to 25 drugs used to treat only two diseases," says Gabriela Chaves, one of the study's authors and a researcher at the ENSP. "The government buys many other drugs for dozens of other diseases. The impact of the European Union proposals on the intellectual property chapter may reflect a much higher expenditure than the estimated R$1.9bn per year estimated by the research."

The two main issues that the study highlights are EU proposals that would see the four nations extend patent terms for medicinal products to compensate for delays in winning regulatory approval and introduce data exclusivity for an unspecified period. Currently Mercosur markets do not have any data exclusivity provisions for pharmaceuticals.

The report notes that Mercosur countries have already signed up to the World Trade Organization Trade Related Aspects of Intellectual Property (TRIPS) agreement, and says that the EU's demands go beyond TRIPS requirements and would jeopardize national health systems and access to medicines.

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Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
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
Bayer HealthCare Pharmaceuticals' ciprofloxacin inhalation powder for reduction of exacerbations in non-cystic fibrosis bronchiectasis adult patients (≥18 years of age) with respiratory bacterial pathogens	Antimicrobial Drugs	Nov. 16
Bulk drug substances nominated for inclusion on the Sec. 503A Bulks List and drug products nominated for inclusion on the list of drug products that present demonstrable difficulties for compounding under Sec. 503A and 503B ("Difficult to Compound List")	Pharmacy Compounding	Nov. 20-21
Discussion of 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

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