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EU Gets Going On EMA Move To Amsterdam, Insisting The UK Pay €400m Removal Bill

IAN SCHOFIELD ian.schofield@informa.com

The European Commission has drafted legislation formally naming Amsterdam as the new seat of the European Medicines Agency, which has to move out of London as a result of the UK's decision to leave the EU.

The legislation also reiterates the EU's position that the UK is responsible for meeting all the costs incurred in the relocation of the EMA and the other London-based EU agency, the European Banking Authority.

The Dutch capital was chosen as the EMA's new home by a vote of EU27 member state ministers on Nov. 20, pipping Milan to the post by a drawing of lots. A total of 19 countries had originally bid to host the agency. The EBA is going to the French capital Paris. *(Also see "Amsterdam 'Ticks Many Of Our Boxes,' Says EMA Head After Dutch Win Race To Host Agency" - Pink Sheet, 21 Nov, 2017.)*

Now the names of the new host cities have to be enshrined in legislation, which the commission is doing by drafting two regulations that will amend the medicines legislation, Regulation (EC) No 726/2004. The regulations will need to be approved by the European Parliament and the Council of the EU, but this is expected to be a formality.

The commission said it was "acting swiftly in order to provide legal certainty and clarity, ensuring that both agencies can continue to function smoothly and without disruption beyond March 2019." It added that the parliament and council were "expected to give priority to the handling of these legislative proposals."

Both regulations state that the relocation of the agencies will have "budgetary implications," particularly in view of the costs relating to the early termination of the current rental contracts for their London premises.

In the case of the EMA, these costs are likely to be substantial. There is understood to be no "break clause" in the agency's rental contract, and given that the lease stretches to 2039, the outstanding amount to be paid has been estimated to be as much as €400m, although the commission said the total cost could not be determined at present as it would depend on a number of factors.

There will also be costs relating to the move itself and the installation of the agency in the new premises in Amsterdam – and the UK looks likely to be asked to foot the bill. The regulations repeat what is stated in the council's Brexit negotiating directives of May 22, 2017: that the UK should "fully cover the specific costs related to the withdrawal process, such as the relocation of the agencies or other Union bodies."

It is likely that these costs will be part of the financial settlement to be paid by the UK for its outstanding EU liabilities.

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Chris Keeling | Tel: +44 (0) 20 3377 3183 | Mobile: +44 (0) 7917 647 859
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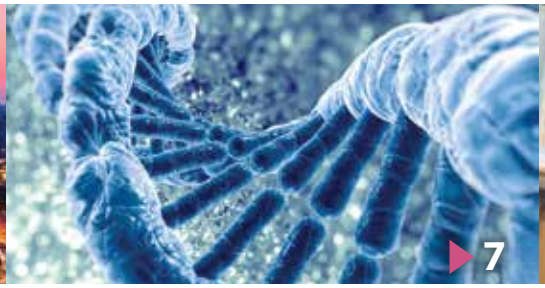
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The amount of this settlement has yet to be decided, but it is thought to be in the region of €50bn.

PRE-FINANCING FROM EU BUDGET

The commission says that some of the relocation costs may have to be pre-financed from the EU budget before the financial settlement is agreed, no doubt because the EMA needs to begin the move to Amsterdam as soon as possible so that it is up and running by March 30, 2019.

"In this respect, the commission will assess possible additional funding needs to be channelled through the EU budget in cooperation with the European Medicines Agency," it says. It will present relevant proposals to the European Parliament and the Council as part of the annual EU budgetary procedure for 2019, "and if necessary for 2018. This concerns for instance the costs related to the move itself."

A commission spokesman told the *Pink Sheet* that as negotiations are still under way, no further information could be provided at this stage. "I would just point out as well that we are seeking to make sufficient progress on the financial settlement in the first phase of the negotiations, in order to move to phase two. Discussions will, of course, continue on this topic in the second phase too," the spokesperson said.

In addition, the costs relating to the agency's installation in the new premises will be presented in the context of the "building procedure" set out in EU legislation, which requires prior approval from the parliament and council before contracts related to building projects are concluded. "This procedure is expected to be launched as soon as possible (at the latest in early 2018)," the commission says in the regulation.

It adds that to ensure the proper functioning of the EMA in its new location, a headquarters agreement needs to be concluded before it moves in. In order to give the agency sufficient time to relocate, "this Regulation should enter into force as a matter of urgency."

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

Industry Chief Calls For "Honesty And Pragmatism" On EMA Move

MAUREEN KENNY maureen.kenny@informa.com

"At the moment no one is really being honest about the challenges of this transfer." That's what Mike Thompson, chief executive of UK's main pharmaceutical industry body, the ABPI, thinks about the current activity relating to the Brexit-induced move of the European Medicines Agency from London to Amsterdam.

Speaking at a public hearing of the House of Commons business, energy and industrial strategy committee on Dec. 5, Thompson called for honesty and "real pragmatism" during the negotiations.

"We are now trying to move 950 people from Canary Wharf to Amsterdam – already 200 have said they won't go, so it is already a 20% problem," he said. This echoes what the EMA itself has said.

The relocation task is complicated further by the fact that the new premises that are being built to house the agency – the Vivaldi Building in the Zuidas district of Amsterdam – will not be ready for occupancy when the UK leaves the EU at the end of March 2019.

Thompson moved on to specific challenges relating to the transfer, including housing for EMA staff and education for their children. "The property market in Amsterdam grew 15% last year, it is one of the hottest property markets. There are 600 kids at EMA who will need to be found international schools. I have to tell you I think there will be very serious issues affecting that sort of transfer. We all know that where one parent working in an organization is offered job overseas, if you can't get kids into school, then people make choices based on family needs, not professional needs. So at the moment no one is really being honest about the challenges of this transfer. I hope that as we get into phase 2 [of the Brexit negotiations] there can be some real pragmatism here."

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Some people should be allowed to stay in London and work out of the existing EMA building in the Canary Wharf area of the UK capital, suggested Thompson. "There is a long lease on Canary Wharf, there will be a number of people who won't choose to move. We need to have a pragmatic agreement, we need to be generous, but we need to have a number of people who continue to work from the EMA out of Canary Wharf, otherwise quite frankly the EMA will not be able to fulfil all its duties."

"As soon as we are out of the heavy negotiation we need to get into something that is much more pragmatic," the ABPI head told MPs.

Thompson was in fact responding to a question about whether there was a likelihood that people who decide not to move with the EMA might go for jobs in industry. He answered as follows: "There will be some opportunity at the margins, but I would say that at the mo/ment we all know is there is a negotiation going on and some hardball is being played." He then issued the call for pragmatism and honesty.

Thompson, it seems, is trying to inject some urgency into proceedings.

The EMA is making much of the fact that, before the vote, Amsterdam was a favored potential destination for the agency, with a staff survey suggesting some 81% of the workforce would consider moving there. However, the agency has said on numerous occasions that it has to be prepared for lower than hoped-for retention rates, most recently at the press conference on Nov. 21, the day after Amsterdam won the bid to host the agency.

Remote working, too, is on the EMA's radar as a potential means of helping keep retention levels as high as possible, the agency's top two officials said at the press conference.

The *Pink Sheet* had asked whether it would be possible for non-UK EU nationals currently working for the EMA in London to continue living there and commute to the Netherlands. EMA deputy executive director Noel Wathion replied: "One aspect we are also looking into is extended teleworking which could be abroad, so not only in the Netherlands but in any other country. We have to take into account that staff may decide, for instance, that their children may stay longer in UK schools depending on where exactly they are in the whole education system, so these are aspects that we will be looking at with the aim of trying to retain as many staff as possible."

On the same topic, EMA executive director Guido Rasi raised the possibility of transition rules for staff retention, "such as working remotely which is not possible for meetings management but for many other activities it is feasible". He called for "flexibility, certainly", saying "they have to lift some of the current rules which work well in a normal setting but not in exceptional circumstances."

Wathion said the agency needed to look further into the capacity of local schools as well as at staff accommodation options. "Frankly speaking," he said, that was "not really addressed in any of the bids, so we will have to see." The Netherlands claims to be one of the few member states with a rapidly expanding capacity at international schools.

TWO OFFICE MOVES, NOT ONE

Bidding member states were able to propose a temporary building as well as permanent one. As detailed in the Dutch government bid letter and bid book, the relocation to Amsterdam will in fact involve not one but two office moves.

The conference facilities will be available at the Vivaldi Building as of April 1, 2019, but EMA staff will initially be housed in temporary offices close by, in some cases for six months, i.e., until October 2019. "The remaining office floors holding workstations will become available at a regular pace in the six months following the [UK} removal date. The temporary office will be available as of 1 January 2019, or earlier if required by EMA," according to the Dutch government.

> "They have to lift some of the current [staffing] rules which work well in normal setting but not in exceptional circumstances."
> – Guido Rasi, EMA executive director

This is clearly not ideal. Rasi referred to it at the press conference as a major challenge. Wathion said: "We'll have to [work] with the Dutch authorities to see how this can be [done] in the best possible way."

SEAT AGREEMENT

With regard to the headquarters or "seat" agreement that now has to be negotiated and signed by the EMA and the Dutch government, Wathion said the agency would take "as a starting point" the commitments made by the Dutch authorities in their offer to host the agency. Transparency would be key, he said. "We need to make sure the general public is fully aware of progress being made, so [we] will discuss with the Dutch authorities the use of common communication tools where we can track progress with all the different activities to have a successful relocation by March 2019."

"At the political level, we need probably measures and procedures to speed up the building, the relocation and seat agreement," Rasi remarked. In this context, he said, there could be "difficult processes with many steps".

The Dutch government has said the agreement could be signed "as early as May 2018".

A collaboration framework also has to be agreed, Wathion said, "with dedicated governance structure, decision making process[es], clarity about roles and responsibilities, transparency, communication, etc". The EMA was due to meet with the Dutch authorities in the days following the Nov. 21 press conference to agree on that framework.

EXISTING UK STAFF

It was assumed that after Brexit the EMA would by necessity lose the UK nationals who currently work for it, but that appears not to be a given. In response to questions from the *Pink Sheet*, the agency said that while there remained uncertainty as to what will happen with British staff following Brexit and that "issues around their employment after Brexit still need to be clarified", it hoped it would to be able to find what it described as an "EU-wide solution" for British staff. It gave no further details.

In 2016, UK nationals made up 6.8% (about 60) of the agency's 897-strong workforce.

The EMA is working on a roadmap that it hopes will enable it to meet the deadline of the end of March 2019.

It's going be a long and difficult 16 months.

From the editors of Scrip Regulatory Affairs. Published online December 6, 2017

CVS/Aetna Deal Faces Challenge of Appeasing Current PBM Clients

COLE WERBLE pinkeditor@informa.com

The vertical mega merger is unveiled as the formula for the future: a new combination of business partners designed for a changing era in healthcare and payer concerns about hospital costs: a way to prepare for the future and shape the future at the same time.

The $77 billion **CVS Health Corp.-Aetna Inc.** merger?

No, a failed antecedent from a generation-plus ago (1985) – the proposed merger of American Hospital Supply with one of its biggest customers, **Hospital Corporation of America**.

The relevance of the failed event to CVS/Aetna?

One of the key factors behind the breakup of the previous vertical merger was a revolt among American Hospital's other customers, hospitals who viewed Hospital Corporation of American as among their most feared commercial competitors.

There are few if any of the active decision-makers left from the short and intense fight that scuttled the 1985 vertical merger, but some of the basic business thinking is primal and likely to persist. Why should other insurers pay for CVS pharmacy benefit management services (price negotiations and administrative services) if there is a lingering fear that they may not be getting as good a price or as big a chunk of rebates as Aetna? Is their volume of drug purchases through CVS/Caremark going in some way to support their competitor?

The reaction of other insurers/clients to the CVS PBM business is one of the issues to watch as the current proposal winds its way towards a planned closing in the second half of next year. A related marker to watch: how successful can **Express Scripts Holding Co.** be as the independent representative of insurer clients?

CVS Health President/CEO Larry Merlo anticipated that fundamental concern about the state of an important ongoing piece of the business. He referred to that concern among a list of "important points" at the end of his short summary of the business rationale for the merger during the Dec. 4 conference call on the deal.

In a staccato, emphatic tone, Merlo declared "this transaction will not – in any way – diminish the strong relationship that CVS and Aetna have with our clients and their healthcare partners. Nor will it reduce the value that we both create for them every day."

Merlo pointed out that "CVS has a long history of developing solutions that deliver on the cost-quality access goals of our partners and we see no reason not for that to continue into the future."

The CVS top exec further observed that the previous integration of the CVS retail base with the Caremark benefit management business provides a model of a sustainable vertical integration.

"As we have shown with the integration of CVS and Caremark," Merlo told the conference call, "we have the ability to integrate where needed while maintaining the necessary firewalls in order to protect client data and ensure competition."

There is also the outside model of UnitedHealthCare's internal data analytics and PBM operation, Optum, that serves as a counterweight to the planned merger.

A new CVS/Aetna will face some big paybacks and promises: $49 billion in already arranged financing to cover the cash part of the deal and near-term savings and growth of $750 million by the second full year after the deal. That has to focus attention on improving Aetna's cost control over pharmaceuticals by assuring that it gets the best deal from CVS PBM negotiations and similarly assuring that the retention of rebates and fees is greatest for the Aetna business.

Aetna Chairman/CEO Mark Bertolini suggested that the key to the success of the proposed deal should not be read by the business clients but instead by the impact on the patient/consumer – the deal's theme of a remake of the consumer health care experience and the creation of "a new front door to the healthcare system."

Bertolini pointed out that "41% of the health care dollar is pulled out of pocket today by the consumer. Through the right, appropriate site of care, we can offer people a better cost experience, more convenient and local."

So, CVS/Aetna believes it can make the case for the merger around at least some of its current business customers. The firms also have the advantage of not posing the horizontal competition concerns that cool insurer mergers.

Three decades ago, **Baxter International Inc.**, the primary competitor to American Hospital, broke up a revolutionary vertical merger with a cash counter offer for American Hospital (more solid than the potential of new stock in the new merged company) and a strong appeal to other hospitals to shift away to "a strong and independent provider for all hospitals and health providers." *(Also see "Baxter And American Hospital Supply Can Look To $1.5 Bil. Revenue Flow From HCA Contract For 1986-1990; Price Wars May Loom In Supply Field" - Pink Sheet, 22 Jul, 1985.)*

Raising a better offer to CVS/Aetna would be a big task; finding a PBM in the already concentrated field that could counter the proposed deal directly is also unlikely – but keeping CVS Caremark attractive to customers could be a weak spot in the plan. It has happened before.

From the editors of the RPM Report.
Published online December 4, 2017

US FDA May Create Immunology, Neuroscience Centers Of Excellence

DERRICK GINGERY derrick.gingery@informa.com

US FDA Commissioner Scott Gottlieb has two additional centers of excellence already in mind – immunology and neuroscience – should the model implemented for oncology work as planned.

Both, like the Oncology Center of Excellence that launched at the beginning of 2017, would allow experts in the fields from across the various product centers and offices at FDA to increase collaboration and potentially speed product reviews.

Gottlieb told the House Energy and Commerce Subcommittee on Health Nov. 30 that the agency was "contemplating" both potential centers. "It's very important that we get it right in setting up oncology since this is our test case and our first model for this," he said during the hearing, which was called to discuss ongoing implementation of the 2016 21st Century Cures Act.

Gottlieb also discussed a potential expansion of accelerated approval during the subcommittee hearing.

The Cures law allowed for creation of the Oncology Center of Excellence, which launched in January. *(Also see "FDA's Pazdur Jumps Over To New 'Moonshot' Role" - Pink Sheet, 29 Jun, 2016.)* Cures also requires FDA to create multiple iterations of what were called "intercenter institutes." *(Also see "Cures Bill Authorizes 'Intercenter Institutes,' But Will US FDA Create Them?" - Pink Sheet, 28 Nov, 2016.)*

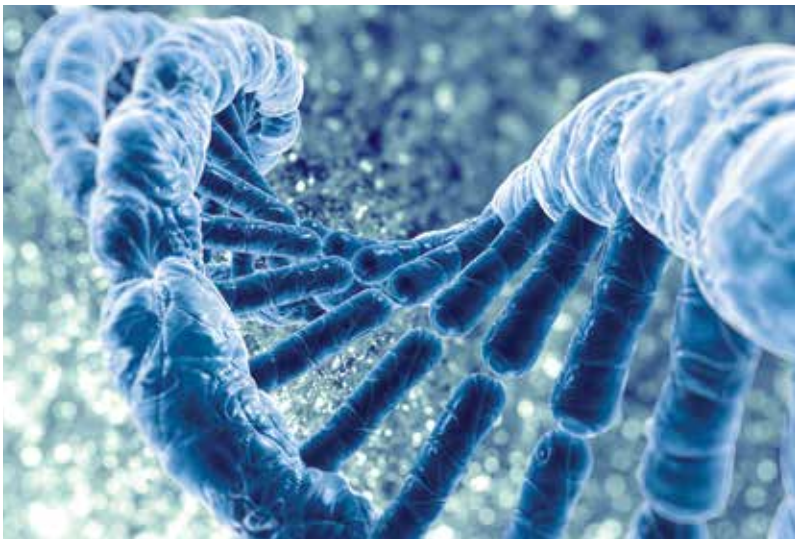
FDA would not comment on when a decision could be made on creation of the immunology and neuroscience centers. Gottlieb said during the hearing that the agency believes "that this kind of center approach represents the future."

The two sectors seem to fit in terms of cross-center collaboration, in part because combination products could emerge in both settings. For neurology, the agency has divisions in the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health that oversee the products. CDRH and the Center for Biologics Evaluation and Research also have divisions devoted to immunology.

Reviews of drug-device combinations have been problematic in part because the review timelines often are not congruent. *(Also see "Combo Product Review Pilot At US FDA Will Offer All Applications Intercenter Consults" - Pink Sheet, 20 Dec, 2016.)* FDA officials also have said the next center of excellence likely will grow from areas with a lot of combination product activity. *(Also see "FDA Tussles With Combination Products, Fires Up Oncology Center Of Excellence" - Pink Sheet, 26 Jun, 2017.)*

There has been a lot of speculation as to where the next center of excellence could be placed. Neurology, infectious diseases, and cardiology were offered as potential next steps by the Friends of Cancer Research, which proposed the original Oncology Center of Excellence idea. *(Also see "FDA 'Intercenter Institutes' Legislation Headed For Senate Mark-Up" - Pink Sheet, 28 Mar, 2016.)*

And Office of New Drugs Deputy Director Peter Stein has said FDA also was thinking about whether a rare disease center of excellence was needed. *(Also see "US FDA Drug Office Reform: 'Everything' Is On The Table" - Pink Sheet, 15 Nov, 2017.)*



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> "The two sectors seem to fit in terms of cross-center collaboration, in part because combination products could emerge in both settings.

FORMER COMMISSIONERS LIKE IDEA

Former FDA Commissioner Robert Califf agreed that immunology and neurology were good choices for additional centers of excellence. He also told the Pink Sheet that he hopes cardiovascular disease will "evolve in this direction."

While the biomedical world is grouped by disease type, stage of life and body part, "the FDA was configured by 'product type' and that made sense in the 'good old days,'" said Califf, who now is vice chancellor for health data science at Duke University and an advisor for Verily Life Sciences.

Califf added that a reservoir of knowledge by product type still is needed, but as medicine evolves into a patient- or person-centered world for benefit, risk and safety assessment, FDA should align with the "real world."

"People generally have concerns about the same clinical outcomes regardless of product type, and there is real value in providing consistent advice and decision making," Califf said.

Mark McClellan, also a former FDA commissioner as well as a former CMS administrator, told the Pink Sheet that immunology and neurology make sense as centers of excellence because there are examples of combination products and targeted immunotherapies in those areas where a cross-disciplinary approach would help.

But McClellan, currently director of the Duke University-Robert Margolis Center for Health Policy, also has warned that reorganizing FDA to focus on diseases rather than products may not be the most efficient use of resources in all cases. *(Also see "Don't Rush To Reorganize FDA, McClellan Says" - Pink Sheet, 29 Feb, 2016.)* Former Office of New Drugs Director John Jenkins also has advised against making too many organizational changes. *(Also see "Multiple 'Centers of Excellence' At US FDA Could Create Review Inefficiencies – Jenkins" - Pink Sheet, 19 Dec, 2016.)*

OND is in the midst of a restructuring, where many review practices could change. *(Also see "US FDA Drug Office Reform: 'Everything' Is On The Table" - Pink Sheet, 15 Nov, 2017.)*

FUNDING REMAINS IMPEDIMENT, MCCLELLAN SAYS

While McClellan was optimistic that the OCE model could work in other diseases, he also said that it will require the necessary funding to realize its full potential.

Cures included a mandate that NIH transfer money to the agency for cancer-related activities, but no statutory authority was included to allow the inter-agency moving of funds. That has left the OCE without any Cures-related money.

McClellan said the OCE has not "fulfilled its full potential yet because the funding hasn't been able to be worked out." Without the money, it will be difficult for the agency to use the model in other areas, he added.

The House fiscal year 2018 appropriations bill would fix the funding problem *(Also see "FDA's Budget Flat In House Bill, But Path For 'Cures' Funding Cleared" - Pink Sheet, 28 Jun, 2017.)*, but it has not been passed.

FDA also ran into problems receiving other Cures-related funds, although that has since been resolved. *(Also see "US FDA Still Waiting For Cures Money, Woodcock Says" - Pink Sheet, 25 Apr, 2017.)*

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

How To Conduct A Multi-Company Trial For Rare Pediatric Diseases

BRENDA SANDBURG brenda.sandburg@informa.com

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> "People should really look at this draft guidance. very smart approach for rare diseases," former FDA Commissioner Robert Califf tweeted.

The US FDA is casting a spotlight on a new approach to the development of drugs for rare pediatric diseases in which companies would test multiple product candidates in the same clinical trial.

FDA and the European Medicines Agency suggested this course of action in a joint proposal to promote the use of innovative approaches in the development of medicines for Gaucher disease, which was published in July. FDA is advancing the idea with a draft guidance describing how this strategy could be implemented.

The draft guidance, "Pediatric Rare Diseases – A Collaborative Approach for Drug Development Using Gaucher Disease as a Model," discusses the key features of a multi-arm, multi-company trial to demonstrate safety and efficacy in treatment-naïve pediatric patients with Gaucher disease Type I, including the main inclusion criteria, relevant age groups, suggested efficacy endpoints and study duration.

The agency said the general principles presented in the guidance may be extended to other areas of drug development in rare diseases.

FDA announced the draft guidance in a Federal Register notice slated for publication Dec. 7. It notes that the guidance was originally a document developed as part of a strategic collaboration

between FDA and EMA to enhance drug development for Gaucher disease. The joint plan was released for public comment in 2014.

FDA said its draft guidance is an updated version of the document with no fundamental changes to the original content. Comments on the guidance are due 60 days from publication.

The proposal is getting much more attention with the release of the draft guidance, which FDA highlighted in a news announcement on its website.

"Working with our European regulatory colleagues at the EMA, the FDA has drafted an approach to pediatric rare disease drug development that could eliminate the need for certain clinical studies and, when pediatric clinical studies are needed, could reduce the total number of patients who would receive a placebo instead of a potentially helpful drug," Janet Woodcock, director of the Center for Drug Evaluation and Research, stated.

Former FDA Commissioner Robert Califf praised the guidance in a Twitter post. "People should really look at this draft guidance. very smart approach for rare diseases. With ubiquitous EHR's we should have: 1) great system for finding rare dz patients so they can participate in trials & be helped by tx; 2) a tremendous post-market system," he wrote.

WILL ADDITIONAL CLINICAL TRIALS BE NECESSARY?

When the EMA and FDA joint plan was released, the European Federation of Pharmaceutical Industries and Associations welcomed its consideration of alternative clinical trial designs for small trial populations. However, it said the approach raises regulatory and legal questions, such as the eligibility for pediatric rewards and incentives, and whether an applicant would be expected to develop additional clinical studies in pediatric patients depending on the specific product and mechanism of action. *(Also see "Multi-Company, Multi-Product Clinical Trials On The Cards For Rare Pediatric Diseases" - Pink Sheet, 4 Jul, 2017.)*

In comments on the draft joint proposal, the Biotechnology Industry Organization (now the Biotechnology Innovation Organization) encouraged FDA to publish the collaboration approach in the Federal Register for public comment so it could be formally considered as agency guidance.

BIO asked the agencies to clarify aspects of the proposed multi-product, multi-company study, including the requirements governing "sponsorship" and the eligibility of individual products for specific designations, such as orphan designation. It also urged the agencies to discuss with industry ways to establish and leverage the utility of registration studies.

EXTRAPOLATION OF EFFICACY DATA

Gaucher disease is a lysosomal storage disorder, an inherited disease that causes the build-up of fatty substances in the body due to the lack of enzymes to break them down. It is estimated to affect 6,000 individuals in the US. The guidance notes that the current standard of care in the pediatric Gaucher population in the US is enzyme replacement therapy (ERT).

The draft guidance says that previous approval of ERT for Gaucher disease in adult patients has been based upon demonstrated clinical improvements in hepatosplenomegaly and improvements in biochemical endpoints (hemoglobin and platelet levels).

> "For drug development in pediatric rare diseases, it may be necessary to develop, validate and employ age-specific endpoints."

"For drug development in pediatric rare diseases, it may be necessary to develop, validate and employ age-specific endpoints," the guidance states.

FDA notes that extended follow-up in a prospective study is necessary to evaluate the long-term safety and efficacy of treatment on disease manifestations in pediatric populations. The agency says patient registries are an adjunctive tool for monitoring safety and efficacy, and it recommends across-registry agreements on a uniform set of core data elements to be collected by all existing or future Gaucher disease registries.

The guidance says extrapolation of efficacy can be considered when the course of the disease and the expected response to a drug product would be sufficiently similar in the pediatric and reference population, i.e., adult or other pediatric age population.

Whenever new studies in children are deemed necessary, modeling and simulation should be used to optimize pediatric studies (e.g., design, sample size, starting doses, timing of sampling, and number of samples) and particularly to inform the dosing rationale, the guidance states.

MULTI-ARM, MULTI-COMPANY TRIAL

The guidance includes a two-and-a-half-page table detailing the strategy for designing a multi-arm, multi-company drug development program. It applies only to systemic (non-neurological) manifestations of Gaucher disease in treatment-naïve patients with Type I and Type III phenotypes across all pediatric ages. It is not intended for neurological manifestations of the disease, for which there are currently no approved drug products.

"Although such a program can be very challenging, the aim of the strategic plan is not only to facilitate agreement on individual applications, but also to address the feasibility of developing multiple drug products for a rare disease in a time-efficient manner," the guidance states.

The proposed study design is a double-blind, controlled, randomized, multi-center, multi-arm, multi-company noninferiority or superiority trial to evaluate the efficacy and safety of "product A," "product B," product C," etc., compared to a single ERT drug product in pediatric patients with Gaucher disease Type I and Type III.

The main objective would be to evaluate noninferiority or superiority of the new drug product(s) to an approved ERT treatment. The study population would include male and female pediatric patients, from birth to younger than 18 years. And the treatment period would be two years with long-term monitoring of primary and

secondary endpoints and safety conducted in an extension study.

The guidance says relevant endpoints should be chosen based on the mechanisms of action of the selected drug products and should consider the heterogeneity of the pediatric population.

PROMOTING NOVEL TRIAL DESIGNS

The draft guidance reflects FDA's interest in novel clinical trial designs. It is in line with draft guidance the agency issued in November on regenerative medicine therapies for serious conditions. In that document, FDA said it might be useful for sponsors to compare several different investigational agents to each other and to a common control in studies of therapies to treat rare diseases. *(Also see "Regenerative Medicine Clinical Trials: US FDA Supports Studies Comparing Multiple Agents" - Pink Sheet, 16 Nov, 2017.)*

This kind of approach has been used in the oncology arena. For example, in the I-Spy 2 Phase II platform trial, 12 therapies from nine sponsors were evaluated in eight genetically defined subgroups.

FDA's Woodcock and Office of Biostatistics Director Lisa La-

> The draft guidance aligns with a recent regenerative medicine guidance suggesting it might be useful for sponsors to compare several different agents to each other and to a common control in studies of therapies to treat rare diseases.

Vange touted the use of master protocols to study multiple therapies and/or multiple diseases in a New England Journal of Medicine article published in July. *(Also see "Master Protocols Are Both Welcome And Inevitable – US FDA's Woodcock" - Pink Sheet, 6 Jul, 2017.)*

Published online December 1, 2017

NEW PRODUCTS

FDA's NDA And BLA Approvals: Lonhala Magnair, Ozempic

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				
Hospira	*Epinephrine*	Epinephrine injection to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.	S, 7	11/29/2017
Indivior	*Sublocade* (buprenorphine)	Once-monthly subcutaneous injection to treat moderate to	P, 3	11/30/2017
Sunovion	*Lonhala Magnair* (gycopyrrolate)	Inhalation solution for the long-term maintenance treatment of airflow obstruction in patients with chronic	S, 3	12/5/2017
Novo Nordisk	*Ozempic* (semaglutide)	Once-weekly injection of the glucagon-like peptide (GLP-1) receptor agonist as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.	S, 1	12/5/2017
New Biologics				
Mylan	*Ogivri* (trastuzumab-dkst)	Biosimilar to Genentech's Herceptin to treat HER2-overexpressing breast cancer and the treatment of		12/1/2017

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

Keytruda: US FDA Reflects On Lessons Learned From Failed Myeloma Studies

SUE SUTTER sue.sutter@informa.com

The troubling mortality results from two multiple myeloma trials of **Merck & Co. Inc.**'s PD-1 inhibitor *Keytruda* (pembrolizumab) suggest important lessons for future immunotherapy studies of combination regimens, US FDA officials say.

The higher rate of death in the pembrolizumab-containing arms in both the KEYNOTE-183 and KEYNOTE-185 studies underscores the importance of randomized, controlled trials and the need for sponsors to consider possibly incorporating control arms in earlier-phase studies to assess toxicity.

In addition, the pembrolizumab experience highlights the need for a thoughtful and considered approach to development, including ensuring that there is a good rationale underlying the combination regimen proposed for testing, agency staff said.

At two recent meetings, Richard Pazdur, director of FDA's Oncology Center of Excellence, and Nicole Gormley, a clinical team leader in the Office of Hematology and Oncology Products, weighed in on their views of lessons learned from the two failed Merck trials.

In July, FDA imposed a clinical hold on the two Phase III studies (as well as a partial clinical hold on a cohort in KEYNOTE-023) due to an increased risk of death for patients receiving the immune-checkpoint inhibitor with immunomodulatory agents compared to the control group. Merck had halted new patient enrollment in the two studies a month earlier due to the mortality imbalance.

KEYNOTE-183 was a randomized, controlled trial of **Celgene Corp.**'s thalidomide analogue *Pomalyst* (pomalidomide) and low-dose dexamethasone with or without pembrolizumab in patients with relapsed and refractory multiple myeloma who had received at least two prior lines of therapy. Patients on the pembrolizumab arm had a 61% increased risk of death compared to the control group.

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> "Our paradigm of ... let's just add something onto existing therapy may not be the correct." – OCE Director Pazdur

In KEYNOTE-185, newly diagnosed multiple myeloma patients who were ineligible for autologous stem cell transplant were randomized to Celgene's *Revlimid* (lenalidomide) and low-dose dexamethasone with or without pembrolizumab. Patients in the pembrolizumab arm saw a doubling in their relative risk of death compared to the control group.

In an Aug. 31 statement, FDA released detailed results from the two KEYNOTE studies and said the agency was working with sponsors of other PD-1/L1 inhibitors to examine other trials in which the checkpoint inhibitors were being studied in combination with other agents for treatment of hematologic malignancies. *(Also see "FDA Eyeing Other PD-1/L1 Drugs With Clinical Hold On Keytruda Myeloma Trials" - Pink Sheet, 31 Aug, 2017.)*

The agency's action led to partial clinical holds on other studies, including some multiple myeloma combination trials in the CHECKMATE development program of **Bristol-Myers Squibb Co.**'s PD-1 inhibitor *Opdivo* (nivolumab). *(Also see "Deciphering US FDA's Keytruda Safety Announcement" - Pink Sheet, 25 Sep, 2017.)*

MORTALITY DATA AN 'AHA' MOMENT

The mortality results from the two KEYNOTE studies surprised and dismayed industry, clinicians and FDA, resulting in soul searching for the reason behind the adverse findings and how these results may inform future combination studies.

Speaking from the audience during a panel discussion on combination therapies at the recent Friends of Cancer Research (FOCR) annual meeting, Pazdur said one of his biggest disappointments in 2017 was seeing the survival curves from the two pembrolizumab trials in multiple myeloma – results which were not a chance finding. "We saw in two trials almost a doubling in the deaths," Pazdur said, describing it as "one of those 'aha' moments."

The OCE director asked what has been learned from the pembrolizumab experience in multiple myeloma and proceeded to partially answer his own question.

"Our paradigm of … let's just add something onto existing therapy may not be the correct," Pazdur said. "That's probably more for cytotoxic drugs; it probably doesn't work for immunotherapies." He noted that in the pembrolizumab studies three drugs with immunological properties were being used together.

"That is a sobering awakening that has not been well discussed in the oncology community," Pazdur said, adding that he hoped it would be discussed at the American Society of Hematology's annual meeting in Atlanta, which starts Dec. 7.

Although the ASH program does not list any presentations specific to the KEY-

NOTE-183 and -185 findings, the safety profile of immune-checkpoint inhibitors in blood cancers seems certain to be a focus of discussion given the adverse mortality seen in the KEYNOTE myeloma trials.

In addition, the ASH program lists abstracts from other pembrolizumab studies in different multiple myeloma settings. These include a pilot study in smoldering multiple myeloma, and a Phase II trial of pembrolizumab plus lenalidomide and dexamethasone as post-autologous stem cell transplant consolidation in patients with high-risk multiple myeloma.

TAKE-HOME POINTS FOR FDA

Gormley summarized her take-home points from the pembrolizumab combination therapy trials in multiple myeloma during a Dec. 1 workshop on cardiovascular toxicities in immuno-oncology.

"We've not learned all the lessons yet from this experience and that this is something that is still undergoing active investigation within our agency and with some of the other sponsors, but I think there are several things that we've learned from this," she said.

At the top of Gormley's list was the importance of having randomized, controlled data.

"Oftentimes there's desire to accelerate drug development … with reliance on Phase II trials and things like that, and I think this example really underscores the importance of having randomized trials," she said. "We would not have observed or been able to pick up on the safety signal if the trial had been conducted in a different setting other than a randomized, controlled setting."

Gormley's comments echo remarks by Roger Dansey, Merck's senior vice president of oncology clinical research, at the FOCR meeting.

The myeloma study results were "extremely sobering," Dansey said. "We clearly did not expect or ever want such an outcome."

"You look back at what we did, it seemed reasonable at the time just based on the clinical evidence," he said. "And it's clear evidence of why [you] do randomized trials … because without that randomization, in the context of an uncontrolled trial you would not have picked up a signal."

"We would not have observed or been able to pick up on the safety signal if the trial had been conducted in a different setting other than a randomized, controlled setting." – FDA's Gormley

Gormley suggested there could be an opportunity for sponsors to learn about unexpected toxicities sooner in development by incorporating control arms in earlier-phase trials "not necessarily for strong efficacy assessments, but even just evaluating safety differences that would allow you to have more comfort in the safety findings that are being observed."

It may be prudent for sponsors to follow a more measured approach to all of the phases of clinical development, Gormley said, also citing the importance of having a firm understanding and "rational approach to the combinations that are being pursued."

In the multiple myeloma setting, there were very few preclinical models to support the combination of immunomodulators and PD-1 inhibitors, she said. "I think having more information in that setting to really be informed about the mechanism [is] really imperative."

At the FOCR meeting, Kenneth Anderson, a myeloma specialist at Harvard Medical School, said although there were preclinical combination studies of immunomodulatory drugs and checkpoint inhibitors that showed at least additive activity, "I'm not sure in my mind that the preclinical models are adequately reflecting at least toxicities."

The pembrolizumab experience shows that "as we combine therapies, we need to be more vigilant, not less vigilant, for an unexpected toxicity," Anderson said.

More attention also needs to be paid to the how differences in patient population and disease setting may impact an immunotherapy combination regimen's toxicity profile, Gormley said.

"The multiple myeloma patient population in particular generally represents an older patient population that has significant co-morbidities already, and so I think having better attention paid to that aspect," she said.

MOVING AWAY FROM USE IN EARLY DISEASE

The negative results from the two KEYNOTE studies led FDA to restrict the multiple myeloma treatment settings in which immune checkpoint inhibitors could be tested.

Gormley discussed the clinical holds that FDA issue for other PD-1/PD-L1 combination regimens in multiple myeloma after the pembrolizumab mortality results became available.

"Many of the holds …. required that the trials be conducted in a later line of setting, such that we really felt that especially if these trials are going forward they were not appropriate for evaluation in disease settings such as smoldering multiple myeloma or newly diagnosed patients that have available therapeutic options with known clinical benefit," she said, adding that FDA also required informed consent be updated.

FDA also has taken steps to update drug labeling to reflect the adverse mortality results seen in the pembrolizumab studies. On Nov. 30, the agency approved labeling supplements for Revlimid and Pomalyst to add warnings about the increased mortality seen when pembrolizumab was added to standard multiple myeloma treatment with a thalidomide analogue and dexamethasone.

"The addition of a PD-1 or PD-L1 blocking antibody to a thalidomide analogue is not recommended for the treatment of patients with multiple myeloma outside of controlled clinical trials," labeling for the Celgene products states. Keytruda labeling contains similar language.

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HHS Nominee Azar And The Taint Of Industry

MICHAEL MCCAUGHAN pinkeditor@informa.com

It says something about the current reputation of the pharmaceutical industry that the toughest questions during the Nov. 29 Senate Health Committee hearing on the nomination of Alex Azar to be HHS Secretary came from the members of the panel who are at opposite ends of the ideological spectrum: Sen. Elizabeth Warren (D-MA) and Sen. Rand Paul (R-KY).

Warren and Paul don't agree on much. But they both agreed during the hearing that Azar's background as an executive with Eli Lilly raises important questions about whether he can be trusted to perform his duties as HHS secretary in the broader interests of the American public.

Questions about Azar's background industry where not surprise, of course. In general, Azar did an effective job of reframing the discussion away from concerns about a "conflict of interest" from his time at Lilly, focusing instead on the idea that his industry background will help him take effective steps to reduce prescription drug costs. *(Also see "Alex Azar And The Return Of Republican-Style Price Negotiation" - Pink Sheet, 24 Nov, 2017.)*

Azar was especially effective when asked by Sen. Chris Murphy (D-CT) for assurance that he is not joining HHS to promote "PhRMA's agenda." Azar responded by declaring that he doesn't even know what the Pharmaceutical Research and Manufacturers Association agenda is (having left Lilly a year ago). "This is the most important job I will ever have in my lifetime," he declared. Murphy, who began his comments by saying he is "open" to Azar's nomination, sounded satisfied.

The idea that Warren – the champion of the progressive wing of the Democratic party – would be less easily mollified is no surprise. While proclaiming that industry experience is not necessarily disqualifying for government service, Warren asserted that Azar "has a resume that reads like a manual of how to profit from government service." *(Also see "Dems Come Out Swinging During Azar Senate HELP Committee Hearing" - Pink Sheet, 29 Nov, 2017.)*

Her specific line of attack, however, was less predictable – and also very effective at throwing off what had been an otherwise smooth performance by Azar during the hearing. Rather than stick to generalities, she asked Azar about an event that occurred shortly after he joined Lilly: the company's settlement of False Claims Act charges related to the marketing of *Zyprexa* for what was then a record-setting $1.4bn fine. *(Also see "Lilly's Zyprexa Off-Label Settlement: Record Fine, Routine Compliance Deal" - Pink Sheet, 19 Jan, 2009.)*

She pressed Azar for an answer on whether Lilly's settlement was sufficient accountability for the company, given the size of the profits from the underlying conduct – and implied that the company got off lightly because Azar (in effect) switched sides from his role at HHS to head of Corporate Affairs at Lilly. She asked specifically whether Azar's former boss at Lilly (John Lechleiter) should have gone to jail.

In response, Azar struggled between rebutting the premises of the question, defending the integrity of Lilly during his tenure, and emphasizing his role in overseeing prosecutions while at HHS before he joined Lilly.

Sen. Warren's line of attack was less predictable: she asked about Lilly's record-setting settlement of False Claims Act charges related Zyprexa marketing.

First off, he emphasized that he was not involved in the Lilly prosecution at HHS – but somewhat awkwardly said he first learned of it "while interviewing" at Lilly. Azar left the impression that he interviewed at Lilly while still serving as Deputy Secretary at HHS.

Pressed on whether the penalty was sufficient, he repeated Warren's point that it was a record-setting fine at the time – but then added with a smile that another firm (Pfizer) topped that record within weeks. That was also the wrong tone to take, inadvertently supporting Warren's assertion that fines are treated "as a cost of doing business."

His main response was to emphasize that the settlement had a dramatic impact at Lilly. "It was a massive learning and a transformation at the company," he said, adding that no executive at Lilly considers the conduct cited in the investigation to be acceptable. "As we speak, Lilly is the subject of multiple investigations related to insulin," Warren shot back.

It is safe to assume Warren won't vote to confirm Azar under any circumstances. What was more surprising was the threat from Kentucky's Paul to withhold his support for Azar unless he provides a clear and thorough explanation of what it would take to operate a system that allows American consumers to purchase cheaper drugs from Canada or Europe.

Azar, not surprisingly, made it clear that he opposes a so-called "reimportation" program – but Paul was relentless in demanding

a more specific, explicit description of how to overcome the potential safety issues with reimportation. "You are going to have to convince me that you are at least open to it," Paul declared.

Paul was arguably even more withering than Warren in his comments about the pharmaceutical industry's conduct – though he was far less specifically pointed about Lilly's or Azar's. "People think pharma manipulates its power to maximize profits," Paul declared. "Big pharma manipulates the system to keep prices high. It is not capitalism."

When Azar noted that no Republican or Democratic administration has certified that importation can be done safely, Paul cut him off. "That's BS and the American people think it is BS." If "there is a system, we can do it." Otherwise, he suggested, Azar needs to explain why drugs sold legally in Europe and Canada are unsafe.

There are no signs that Azar's nomination is in trouble. While he won't get Warren's vote and may struggle to get Paul's, there seemed to be a general level of comfort from most of the committee with him taking the reins at HHS. But – as happy as the drug industry should be to have Azar running HHS – the theme of the hearing should not be a cause for celebration. At this moment in history, running the US business of Eli Lilly is viewed as a problem – not an asset – for a career in public service.

From the editors of the RPM Report. Published online December 6, 2017

Will Continuous Manufacturing Mean Continuous Generic Delay? FDA Hears AAM's Warning

BOWMAN COX bowman.cox@informa.com

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The organization that represents generic drug companies in the US has taken a hard line against technological innovation in pharmaceutical manufacturing that unfairly increases the quality of brand drugs.

The Association for Accessible Medicines Nov. 17 warned FDA to "remain vigilant" against brand firms' use of new technologies like continuous manufacturing to make drug products of such high quality that generics firms cannot match them using conventional batch methods.

FDA has so far approved two uses of continuous manufacturing technology. The first approval in July 2015 was for **Vertex Pharmaceuticals Inc.**'s new cystic fibrosis treatment, Orkambi (lumacaftor/ivacaftor).

The second was in April 2016 for **Janssen Products LP**'s supplemental new drug application to switch from batch to continuous manufacturing of HIV-1 treatment Prezista (darunavir).

Several generic drug firms have challenged patents for Prezista, which the **Johnson & Johnson** subsidiary has been marketing in the US for more than a decade. *(Also see "J&J To Launch Prezista For HIV Immediately Following FDA Approval" - Pink Sheet, 23 Jun, 2006.)*

AAM's warning came in response to an initiative Scott Gottlieb launched shortly after he became FDA commissioner in May to see how FDA could improve the way it administers the 1984 Hatch-Waxman amendments to the Food, Drug and Cosmetic Act. *(Also see "AAM, PhRMA Renew Rivalry In Hatch-Waxman Public Comments" - Pink Sheet, 21 Nov, 2017.)*

As part of the initiative, the agency requested comments in June on how it should balance innovation and access to drugs – in other words new and generic drugs – and held a public meeting in July to receive verbal comments. Written comments were due Nov. 17. *(Also see "Brand 'Evergreening' Piques FDA Interest, But Solutions Remain Elusive" - Pink Sheet, 19 Jul, 2017.)*

TECHNOLOGY AND ACCESS

At the July 18 meeting, Janet Woodcock, director of FDA's Center for Drug Evaluation and Research, stressed that the agency has "worked over the past four or five years to really enhance manufacturing and modernize manufacturing – and that's both in the innovator space and the generic space."

She said continuous manufacturing is one way innovation can overcome barriers to market access for breakthrough drugs.

Neither AAM CEO Chip Davis nor a half dozen generics industry representatives who spoke at the meeting raised any concerns about continuous manufacturing as a barrier to access.

OLD-SCHOOL RULES

AAM's latest salvo drew a new battle line for Hatch-Waxman over innovation in manufacturing technology, putting the generics sector squarely in the old-school batch mode camp.

"FDA needs to consider that continuous manufacturing will likely be used as a brand protection strategy," AAM commented.

"That is, companies will intentionally design a process so tightly controlled that it is very difficult to make a generic of the product."

The association added that "the fact that the specifications for a process can be tightened does not necessarily mean that tightening those specifications is necessary for assuring the safety and efficacy of a drug."

Rather, AAM said, "differences in the product or the specifications may be insignificant to a patient, but requirements that a generic sponsor demonstrate that the differences are insignificant may create hurdles or barriers to generic approval."

WHY GENERICS MUST COME IN BATCHES

AAM gave several reasons why it's more difficult for generics firms to switch from batch to continuous manufacturing methodologies.

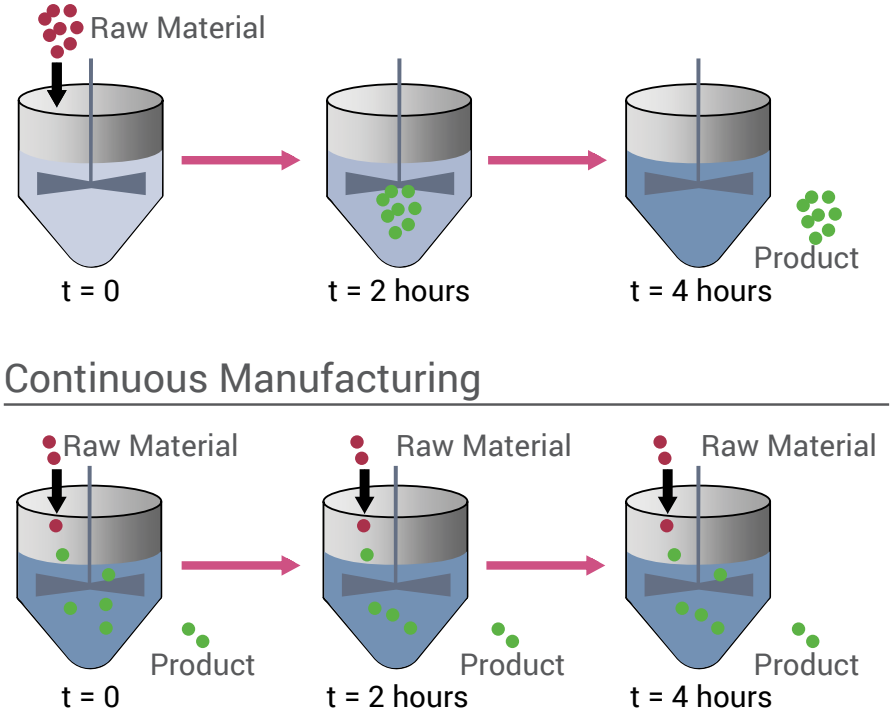
Brand firms can count on a long marketing cycle to pay back investments in continuous manufacturing, while generics firms have little certainty about product lifecycle. Therefore, it may not be practical for them to invest in the requisite product development work.

Another difference AAM noted is that brand firms will dedicate a manufacturing line to one product, whereas generics firms must juggle between multiple products. "This requires flexibility, based on product demand, making adoption of certain technologies specific to a single product impractical," AAM said.

Continuous methods would be particularly challenging for low volume products that generics firms manufacture only once or twice a year, and that therefore would not be worth "the necessary investment for sophisticated technologies."

With many facilities already running at capacity, AAM said generics firms could ill afford the extra lead time, financial investment and reduced margins required to expand capacity with new technologies instead of existing technologies.

The association underscored the difficult nature of generics markets, in which price falls quickly while ingredient costs and supplies fluctuate and regulatory burdens increase.



A simple depiction of two types of manufacturing. Batch manufacturing: the material(s) is charged before the start of processing and the product is discharged at the end of processing. Continuous manufacturing: material(s) and the product are simultaneously charged and discharged from the process, respectively

AN EARLIER CALL FOR MORE DIALOGUE

AAM was called the Generic Pharmaceutical Association when it provided a nearly identical description of the forces preventing generics firms from investing in new manufacturing technologies in February 2016 comments on draft FDA guidance for advancing emerging technology applications to modernize the pharmaceutical manufacturing base.

The guidance spells out how firms can engage FDA's Emerging Technology Team – as Vertex and Janssen did – to help shepherd drug applications through the review process in cases where they intend to use continuous manufacturing or other new technologies. FDA published a final version of the guidance in September. *(Also see "FDA Clarifies Scope Of Its Emerging Technology Program" - Pink Sheet, 2 Oct, 2017.)*

The complaints were all there in the GPhA comments, but the conclusion was different. Despite the uncertain generic drug lifecycle, the need to juggle between multiple products on each manufacturing line, the high utilization rates of those lines and the long lead times that expansion with continuous manufacturing technology would require, GPhA professed an interest in using new technologies to improve quality and availability, concluding that it "strongly supports flexibility and early dialogue with FDA to ensure novel technologies can be integrated as appropriate."

THE PITCH FOR CONTINUOUS

In recent years, advocates in FDA, industry and academia have been promoting continuous manufacturing as faster and cheaper than batch methods. While proponents recognize that process analytical technologies required for continuous methods can attain tighter process control, they have not made a selling point of the resulting ability to meet narrow specifications. *(Also see "Continuous Manufacturing Poised to Disrupt Pharma*

Sector" - Pink Sheet, 29 Jul, 2014.)

And they have argued that generic drug makers ought to be leading proponents.

For example, in June 2014, Woodcock encouraged generics firms to explore the potential of continuous manufacturing.

"Although I recognize that the generic industry works on small margins, it seems to me that your core competency should be manufacturing, and you should be able to manufacture efficiently and more cheaply than your competitors," she told GPhA's CMC Workshop.

By investing in continuous manufacturing, generics firms could increase the reliability and efficiency of their production, she said. "I'll be interested to see if this sector of the industry represented here actually picks up some of these advanced technologies." *(Also see "FDA Talks Up Continuous Manufacturing, Offers Assistance" - Pink Sheet, 29 Jul, 2014.)*

A WIN FOR BATCH METHODS

Coincidentally, on Nov. 21, the day after FDA posted AAM's warning about continuous manufacturing, the agency approved the first generic of Janssen's Prezista. No doubt, **Teva Pharmaceuticals USA Inc.** will be manufacturing its 600 mg darunavir ethanolate tablets using a conventional batch process – as will generic darunavir hopefuls **Lupin Pharmaceuticals Inc.**, **Cipla Ltd.** and **Hetero Drugs Ltd.** when they win FDA approval.

Chalk it up as a win for access.

From the editors of the Gold Sheet.
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Indivior's Once-Monthly Buprenorphine Clears US FDA With Box Warning, REMS

BRENDA SANDBURG brenda.sandburg@informa.com

The US FDA approved **Indivior PLC**'s *Sublocade* (buprenorphine extended-release), the first once-monthly injectable buprenorphine formulation for treatment of opioid use disorder, with a Risk Evaluation and Mitigation Strategy (REMS) requiring administration by a healthcare provider and several postmarket study requirements.

The product is indicated for treatment of moderate-to-severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of seven days. It is administered subcutaneously in the abdominal region using the Atrigel delivery system, which delivers buprenorphine at a controlled rate over a one month period.

The company may eventually get a stronger label. FDA requested the company to conduct a study on use of the drug without a dose stabilization period of sublingual buprenorphine as one of its postmarket requirements.

FDA is also requiring studies to assess the feasibility of administering Sublocade at a longer inter-dose interval than once monthly, to assess which patients would benefit from a higher dose regimen, and to determine the process for moving patients to a monthly dose of Sublocade without the use of a higher dose for the first two months of treatments. The company is also conducting a toxicity study of the NMP component in the Atrigel delivery system. The system is a biodegradable 50:50 poly(DL-lactide-co-glycolide) polymer and a biocompatible solvent, N-methyl-2-pyrrolidone (NMP).

"Sublocade provides a new treatment option for patients in recovery who may value the benefits of a once-monthly injection compared to other forms of buprenorphine, such as reducing the burden of taking medication daily as prescribed," FDA said in a Nov. 30 release announcing the approval.

FDA Commissioner Scott Gottlieb also issued a statement on the approval in which he announced several actions FDA is taking to promote development of new treatments for opioid use disorder. They include providing a framework for development of novel clinical endpoints and a protocol to support a claim that medical assisted treatment at the point of care could lead to reduction in death over a population.

BLACK BOX WARNING ON INTRAVENOUS USE

Indivior expects to launch Sublocade in the first quarter of 2018 at a price of $1,580 per monthly dose. The company currently markets *Suboxone* (buprenorphine/naltrexone) sublingual film. Indivior discontinued *Subutex* (buprenorphine) sublingual tablets in 2011.

The company said it will be offering Sublocade and Suboxone co-pay assistance programs that may reduce initial out-of-pocket costs for eligible patients to as little as $5 each month.

FDA has approved three drugs for treatment of opioid addiction: buprenorphine, methadone and naltrexone.

Another long-acting buprenorphine formulation, **Braeburn Pharmaceuticals Inc.**'s CAM2038, which is proposed for once weekly or once monthly subcutaneous injection, could enter the market around the same time as Sublocade as it has a user fee date of Jan. 19, 2018. The product cleared an FDA advisory panel in October, with 17 members voting for approval of some of the proposed doses and 3 voting against approval of any of the proposed doses. *(Also see " Braeburn's Buprenorphine Clears Advisory Committee, But US FDA Likely To Limit Dosage" - Pink Sheet, 1 Nov, 2017.)*

The agency was concerned about the risk of patients obtaining Sublocade and directly injecting it intravenously since it will be provided in a prefilled syringe with a needle. The label addresses this with a black box warning: "Serious harm or death could result if administered intravenously. Sublocade forms a solid mass upon contact with body fluids and may cause occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, if administered intravenously."

The warning states that Sublocade is only available through a restricted REMS program and that healthcare settings and pharmacies that order and dispense Sublocade must be certified in this program and comply with the REMS requirements.

HIGHER DOSE IS AN OPTION

FDA's Psychopharmacologic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee voted 18 to 1 in favor of approval of the product at a meeting in October. Several members felt the approval should be limited to the lower of two maintenance doses used in Indivior's studies. And some recommended postmarket studies to show the effect of the product in the real world. *(Also see "Indivior's Monthly Injectable Buprenorphine Wins Panel Backing; US FDA May Limit Dosage" - Pink Sheet, 31 Oct, 2017.)*

Indivior proposed that Sublocade, previously referred to as RBP-6000, be available in 100 mg and 300 mg strengths with the 300 mg given monthly for the first two months followed by maintenance treatment of 100 mg or 300 mg monthly based on the clinical condition of the patient.

FDA noted in a briefing document prepared for the committee that the plasma exposures associated with RBP-6000 in the 300 mg monthly dose, after several months of dosing, exceeded those associated with the highest labeled dose of the reference product, Indivior's Subutex. It asked the committee to discuss the role of the 300/300 mg regimen, given the similarity in efficacy results with the 300/100 mg dose. *(Also see "Buprenorphine Injectable Opioid Abuse Treatment: Will REMS Prevent Misuse?" - Pink Sheet, 29 Oct, 2017.)*

The label states that the recommended dose is 300 mg monthly for the first two months followed by a maintenance dose of 100 mg monthly. It adds that "the maintenance dose may be increased to 300 mg monthly for patients who tolerate the 100 mg dose, but do not demonstrate a satisfactory clinical response, as evidenced by self-reported illicit opioid use or urine drug screens positive for illicit opioid use."

PATIENT OUTCOMES STUDY UNDERWAY

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist of the kappa-opioid receptor. Sublocade's efficacy data consisted of two studies, an inpatient behavioral pharmacology study intended to establish the ability of the product to block the effects of an exogenous opioid, 6 mg and 18 mg hydromorphone, and a six-month Phase III randomized, placebo-controlled, parallel group study.

Indivior Chief Scientific Officer Christian Heidbreder said the Sublocade studies were rationally designed beginning with the company's pre-IND meeting with FDA in December 2009. He noted that the blockade study is an example of a study designed in close collaboration with FDA.

The label states that all 12 weeks of the treatment period demonstrated blockade for both 6 mg and 18 mg hydromorphone following Sublocade injections and complete blockade continued throughout the eight weeks' observation that followed the second Sublocade injection.

The Phase III study subjects were randomized into four groups to receive one of two Sublocade injections (first two monthly injections of 300 mg followed by four monthly injections of either 300 mg or 100 mg) or one of two-volume-matched placebo doses. The primary efficacy endpoint was percentage abstinence from illicit opioid use from week 5 to week 24. The key secondary endpoint was treatment success, defined as any subject with ≥80% abstinence from illicit opioid use (urine drug screen plus self-report) between week 5 and week 24.

Based on the cumulative distribution function of the percentage of urine samples negative for illicit opioids combined with self-reports negative for illicit opioid use collected from week 5 through week 24, "regardless of dose, Sublocade was superior to the placebo group with statistical significance," the label states.

"The proportion of patients achieving treatment success (defined as patients with ≥80% opioid-free weeks) was statistically higher in both groups receiving Sublocade compared to the placebo group (28.4% [300 mg/100mg], 29.1% [300 mg/300mg], 2% [placebo]."

In addition to the postmarket studies requested by FDA, Heidbreder said the company is also committed to focusing on patient outcomes with use of Sublocade. He noted that the company's ongoing, prospective, observational RECOVER study is following patients treated with Sublocade for up to 24 months to see if there is an improvement in their quality of life as measured by such factors as their reentry in the workforce and levels of depression and sleep disorder.

"This is as important as showing safety and efficacy," Heidbreder stated.

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US FDA Monitoring Online Forums For Research Into Opioid Misuse And Abuse

MICHAEL CIPRIANO michael.cipriano@informa.com

In addition to combatting the high rates of opioid misuse and abuse, the US FDA is working to identify potential trends that have yet to manifest themselves across the country by monitoring the Internet, Commissioner Scott Gottlieb said.

Speaking Dec. 5 at Informa's FDA/CMS Summit, Gottlieb shed some light on a new agency tactic to fight the opioid epidemic. For the first time, FDA is using a "robust" group of epidemiologists who look to proactively spot utilization and prescribing patterns by scouting online chatrooms, he said.

"That has allowed us to identify some situations … where we think that there might be products that certain people have figured out how to reconstitute in ways that allow them to have abuse potential, but it is not something that everyone is aware of yet," Gottlieb said.

"It is so unique what we are doing in this regard," Gottlieb added. "We are literally looking at data that shows like an uptick in prescribing or utilization of a certain drug in some county, in some state. And what does that mean? What is going on? Is that an indication that we have a burgeoning use trend with a certain product that people in one cluster figured out how to constitute ways [to misuse and abuse it]?"

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> "The complexity of how substances are misused and abused [is] quite ranging, and standard medical sources don't have all that" information, FDA's Dal Pan said.

INSIGHT INTO THE WHO, WHY AND HOW OF ABUSE

Office of Surveillance and Epidemiology Director Gerald Dal Pan also elaborated on the tactic. Speaking with reporters at the summit, Dal Pan explained that the effort is a small piece of the bigger puzzle of understanding opioid misuse and abuse, as it provides insight into the who, why and how of the problem.

"The complexity of how substances are misused and abused [is] quite ranging, and standard medical sources don't have all that" information, he said.

An FDA spokeswoman clarified that social scientists are working with epidemiologists who monitor the Internet. The social scientists work in several FDA's centers, including the Center for Drug Evaluation and Research's (CDER) Office of Communications, she said. The spokeswoman also noted that the social scientists are specifically looking at sites like Twitter and online "drug user boards," such as Bluelight.

Bluelight describes itself as "an international, online harm-reduction community, committed to reducing the harm associated with drug use."

"Bluelight neither condones nor condemns the use of drugs," the website's homepage states. "Rather, we accept that drug use will always exist irrespective of legal status or societal norms. While there is no truly safe way to use drugs, we understand that prohibition and abstinence are not realistic or desirable solutions for everyone, nor have they been adequate in addressing the serious public health concerns associated with drug use."

Gottlieb's discussion of the topic follows a recent slew of announcements about steps FDA has taken on opioids.

Most recently, Gottlieb announced that FDA is developing a protocol intended to support a claim that the availability of medication-assisted treatment when a patient presents with overdose could lead to reduction in death at the population level. He also said the agency planned to issue guidance documents on depot formulations of buprenorphine for opioid dependence, and novel clinical endpoints to support product approvals. *(Also see "Opioid Treatments Could Get Survival Claim As US FDA Develops Protocol" - Pink Sheet, 1 Dec, 2017.)*

FDA also recently published final guidance to assist industry in developing generic versions of approved abuse-deterrent formulations. *(Also see "Generic Abuse-Deterrent Opioids: Comparison To Brand Will Not Require Use Of Control" - Pink Sheet, 21 Nov, 2017.)*

Published online December 5, 2017

Singapore And Colombia Become ICH Member and Observer

FRANCESCA BRUCE francesca.bruce@informa.com

Singapore's Health Sciences Authority has been accepted as a regulatory member of the International Council for Harmonisation in a move that is expected to be a boon for local industry. Meanwhile, Colombia's medicines regulator, Invima, have been recognized as a regulatory observer.

The decisions were taken when the ICH met in Geneva, Switzerland, in November.

The HSA describes its ICH membership as a "significant milestone" that sees the agency join the ranks of big regulators like the US Food and Drug Administration. ICH membership also allows Singapore "first rights" to join ICH expert working groups and to vote on issues discussed at ICH meetings. "This assures that Singapore's views are represented when developing the various ICH guidelines relevant to Singapore, for example the guidelines determining product registration, manufacturing and safety monitoring," said the ICH in a statement.

ICH membership is also good news for local pharma and biotech companies as it makes it easier for them to enter other markets when regulatory requirements are aligned. In addition, Singapore's exports will have priority status in public tenders and procurement systems in some markets, like Hong Kong and Vietnam.

"The ICH membership signals HSA's commitment to align our regulatory requirements and keep pace with international standards. This will facilitate the entry of our local pharmaceutical industry into other markets and bring benefits to patients in Singapore with the faster development of drugs and quicker access to new therapies," said Lam Pin Min, Singapore's senior minister of state for health and transport.

There are now 15 ICH members, including regulators and industry groups (such as Europe's EFPIA and the PhRMA in the US). Other regulatory members in Asia are China's CFDA and South Korea's MFDS, while the PMDA in Japan is a founding regulatory member. Meanwhile, CDSCO in India, TFDA in Taiwan and the National Center in Kazakhstan are regulatory observers.

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> "This will facilitate the entry of our local pharmaceutical industry into other markets and bring benefits to patients in Singapore with the faster development of drugs and quicker access to new therapies" – senior minister of state for health and transport

The ICH has also accepted Colombia's medicines regulator, Invima, as an observer. The regulator has been asked to participate in the next ICH assembly in Kobe, Japan, next year. According to Invima, the news is evidence of Colombia's determination to take part in global discussions to advance pharmaceutical regulations in the country. It also shows that Invima is a regional reference authority.

In Latin America, Brazil's Anvisa became an ICH member in 2016, while Mexico's Cofepris and Cuba's Cecmed actively participate as observers. There are now 24 ICH observers in total.

The Bill & Melinda Gates Foundation was also approved as an observer under the banner of international organization regulated or affected by ICH guideline(s). It joins organizations like PIC/S, the Pharmaceutical Inspection Co-operation Scheme, and IPEC, the International Pharmaceutical Excipients Council.

MULTI-REGIONAL CLINICAL TRIAL GUIDELINES

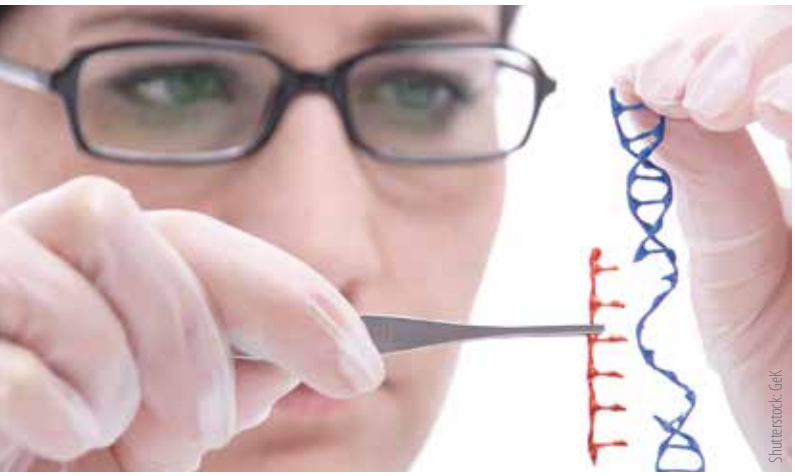
Also at the Geneva meeting, the ICH adopted a major guideline on planning and designing multi-regional clinical trials [MRCTs]. "It is intended that the E17 Guideline will facilitate the acceptability of MRCTs as part of global regulatory submissions in ICH and non-ICH regions, as well as making it easier to seek approval of global trials," said the ICH.

The ICH hopes that the guideline will have a direct benefit for public health by improving the predictability around the approval of clinical trials and using trial data from a broader spectrum of countries and regions. This should speed up market access by cutting marketing authorization delays caused by requirements to carry out studies in local populations.

From the editors of Scrip Regulatory Affairs. Published online December 6, 2017

Gene Therapy Guidances Will Focus On Specific Diseases, Gottlieb Says

MICHAEL CIPRIANO michael.cipriano@informa.com



The US FDA appears to be adding onto its planned slew of disease-specific guidances, with Commissioner Scott Gottlieb announcing that the agency will be releasing "a suite" of such guidances on the development of specific gene therapy documents.

Testifying before the Senate Committee on Health, Education, Labor and Pensions Dec. 7 on the agency's implementation of the 21st Century Cures Act, Gottlieb said the first gene therapy guidance would focus on hemophilia.

"We intend to lay out modern and more efficient parameters – including new clinical measures – for the evaluation and approval review of gene therapy for different high-priority diseases where the platform is being targeted," Gottlieb said.

"Other documents will address clinical areas where there's a lot of interest in using these techniques, such as certain more common single gene disorders. We'll provide innovators with advice on development pathways, including potential accelerated approval endpoints."

The disease-specific gene therapy guidances appear to be separate from the 10 disease-specific guidances Gottlieb previously announced would be coming, which will include development for amyotrophic lateral sclerosis and Alzheimer's disease drugs. *(Also see "FDA's Gottlieb Pushing 'Seamless' Clinical Trials For Faster Development" - Pink Sheet, 11 Sep, 2017.)* These disease-specific guidances are part of a broader reform of the Office of New Drugs (OND), which is in the Center for Drug Evaluation and Research (CDER). *(Also see "Alzheimer's Guidance Coming From US FDA, Part Of Broader OND Reform" - Pink Sheet, 14 Sep, 2017.)* Gene therapies are evaluated by the Center for Biologics Evaluation and Research (CBER).

The commissioner also pointed to a Massachusetts Institute of Technology (MIT) assessment, which estimated that FDA could approve roughly 40 gene therapies by the end of 2022, based on a current pipeline of 932 development candidates. According to the researchers, approximately 45% of the total gene therapies are expected to target cancer, Gottlieb added.

"I can't affirm their assessment," Gottlieb said. "But I can confirm that we're at the early stages of a transformation in medical treatment as a consequence of this new technology. And the benefits are likely to accelerate quickly."

FDA approved its first two gene therapies just this year, giving the nod to **Novartis AG**'s *Kymriah* (tisagenlecleucel) **Kite Pharma Inc.**'s *Yescarta* (axicabtagene ciloleucel). *(Also see "Keeping Track: Another Gene Therapy Approval, Several Priority Review Designations, And Many Resubmissions" - Pink Sheet, 22 Oct, 2017.)*

Gottlieb touted the Cures Act as "sound policy," noting that the legislation has come with timely new policies amid a "turning point" in science.

National Institutes of Health (NIH) Director Francis Collins was also in attendance at the hearing, which took place on the one-year anniversary of Congress reaching an agreement on the legislation, and sending it to then President Obama's desk.

FIXING OCE'S ISSUES

As Gottlieb mentioned the previous week at a House Energy and Commerce Subcommittee on Health hearing, FDA is looking into implementing centers of excellence similar to the Oncology Center of Excellence. *(Also see "US FDA May Create Immunology, Neuroscience Centers Of Excellence" - Pink Sheet, 1 Dec, 2017.)*

The commissioner touted the Oncology Center for Excellence for helping to expedite review of the two approved gene therapies, but also noted there have been issues fully setting it up as a result of insufficient funding.

"We believe that this is the future of the agency though, trying to get these consolidated programs in place, and we are looking to other therapeutic areas we can do this," Gottlieb said. "But I think before we can progress onto other therapeutic areas, we really need to make it work in the oncology setting."

QUIBBLING OVER FUNDING

The hearing mostly maintained a bipartisan attitude throughout the nearly two-hour duration, but one instance where the two sides showed their disagreement came over the Cures Act's funding of NIH and FDA.

Sen. Elizabeth Warren, D-Mass., who voted against the legislation, said that funding was one area in which the bill came up short. She said she would be reintroducing the National Biomedical Research Act, which would provide an extra $50 billion in funding for NIH and FDA. Warren previously introduced the measure

In response to a question about aggregating data across silos, Gottlieb mentioned that FDA would soon take steps to make more clinical data available from approved applications, in a "de-identified" way.

during the Senate markups of the Cures legislation markups, but it only had support from Democrats and was ultimately not adopted. *(Also see "Round 2 'Innovation' Bills Adopted; Funding Fight Ahead" - Scrip, 10 Mar, 2016.)*

Committee Chairman Sen. Lamar Alexander, R-Tenn., said at the end of the hearing that such funding would fall under the jurisdiction of the appropriations committees.

"[The HELP Committee] is the authorizing committee," Alexander said.

"For us to appropriate, say, $50 billion for new funding of the National Institutes of Health is a wonderful aspiration, but that's not what we do," he added. "We decide, for example, whether Dr. Gottlieb should have a new breakthrough path for medical devices. If the appropriations committee were to decide that Dr. Gottlieb should have a breakthrough pathway for medical devices, we would be very upset."

POLICY POTPOURRI

Gottlieb additionally addressed updates in other areas following a slew of other questions from senators about a variety of topics.

The commissioner echoed CDER Director Janet Woodcock's statement from Dec. 6 on the agency's finalizing of a guidance on drug development for rare pediatric diseases. *(Also see "How To Conduct A Multi-Company Trial For Rare Pediatric Diseases" - Pink Sheet, 6 Dec, 2017.)*

"We might not have to rely as much on placebo trials," Gottlieb said. "We might be able to use modeling and simulation to represent the experience of the placebo arm and also allow sponsors to collaborate to try to test multiple drugs in the same clinical trial."

In response to a question from Sen. Todd Young, R-Ind., about aggregating healthcare data across silos, Gottlieb mentioned that FDA would soon be taking steps to make more clinical data available from approved applications, in a "de-identified" way.

"My belief is that if we are making regulatory decisions on the basis of aggregated data that isn't accessible to the public, that is something we should probably try to address," Gottlieb said.

Published online December 8, 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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