REGULATORY UPDATE
Pfizer's EPO Biosimilar Stalls In US On Hospira Compliance Woes, p. 12

LITIGATION
Liability Win For Industry As US Supreme Court Curtails Forum-Shopping, p. 18

CONSUMER PRODUCTS
Oral Contraceptive Switch Advocates Reject User Age As Approval Factor, p. 9

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Criteria Out For EMA's Future Home; Bid Procedure About To Be Approved

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As EU leaders prepare to endorse the procedure for relocating the European Medicines Agency, the Maltese minister for European affairs has announced the six "objective" criteria that potential host countries must meet if they are to have a chance of hosting the agency after the UK leaves the EU.

Speaking at a press conference on June 20, Helena Dalli said that during the meeting of the EU's General Affairs Council that day, the other 27 EU countries had discussed the proposed bidding procedure that will be used to decide the new location of both the EMA and the European Banking Authority. The procedure will be formally adopted on June 22.

> "We are committed to keeping disruption to the function of the agencies to a minimum"
> – Helena Dalli, Maltese minister for European affairs

The EU27 "broadly welcome the process to be followed to ensure that these two important agencies are relocated by the date of the UK's withdrawal," Dalli said. "The procedure aims to ensure that a decision is taken in due course for a smooth and timely relocation of the agencies," and "we are committed to keeping disruption to the function of the agencies to a minimum," the minister declared.

THE CRITERIA

Dalli, whose country currently holds the rotating presidency of the Council of the EU (member state ministers), outlined the six criteria, which are pretty much in line with what has already been reported:

- Assurance that agency can be set up on site and can take up its functions on the date of the UK's withdrawal from the EU.
- Accessibility of the location. This will include fast connections to the host city's airport and good international air links.
- Adequate education facilities for the children of the agencies' staff.
- Access to the labour market, social security and medical care for the children and spouses of the agencies' staff.
- Business continuity.
- Geographical spread.

CONTINUED ON PAGE 4

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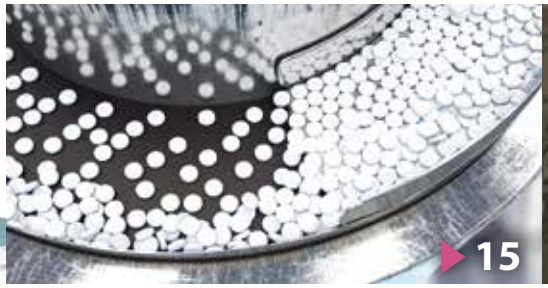
15


18

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Pricing Deregulation: 340B Pharmacy Policy, Medicaid Payment Rules May Be Withdrawn
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Trump administration's drug pricing action plan considers withdrawing guidance and whole or parts of rules that biopharma has opposed.

Biomarkers: FDA/Industry Group Shaping 'Points-To-Consider' On Assay Validation
https://pink.pharmamedtechbi.com/PS120910
Critical Path Institute will deliver white paper on key step in biomarker qualification process: concepts to consider in validating assays to measure the biomarker's performance. White paper has US FDA input, and will in turn help inform agency guidance and internal processes.

Gottlieb Talks Activist Role For FDA In Curbing REMS Abuse
https://pink.pharmamedtechbi.com/PS120914
US FDA commissioner says he would be happy to work with Congress on a legislative solution on the issue, but emphasized his priority is for the agency to develop a system itself to discourage REMS abuse.

Key Indian Panel Go-Ahead For Novartis' Kisqali
https://pink.pharmamedtechbi.com/PS120928
Just months after the US FDA cleared Kisqali, Novartis appears on course to bring the breast cancer therapy to India after a key local expert panel recommended the product for marketing in the country, though the filing route through a local Sandoz company has raised some questions.

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CONTINUED FROM COVER

The first criterion is thought to embrace considerations such as the availability of suitable office premises with the necessary logistics, meeting rooms, archiving facilities, high-performance telecommunication and data storage networks, and IT and other security standards.

Business continuity is a key issue for both the EMA and companies that use its services because any disruptions to the agency's ongoing regulatory operations could raise potential drug safety and other issues.

Although the criteria are supposed to be "objective," the decision-making process may well be dogged by political disagreements, particularly over the geographical spread criterion. This is a reference to the EU's 2003 principle that as many new agencies as possible should be located in member states that joined the EU after that year.

The countries of central and eastern Europe, such as Bulgaria, Croatia, Romania and Slovakia, are particularly interested in the geographical spread criterion as they do not have an EU agency. They feel they deserve one, but they have expressed concern that the proposed bidding criteria are skewed towards the wealthier western European countries and that they will therefore lose out.

Whether this is true is open to debate, but it has been pointed out by the likes of European Commission President Jean-Claude Juncker and EU President Donald Tusk that the EMA is not a new agency and that it needs the assurance of knowing it can continue operating in much the same conditions as it does now as soon as it relocates, in order to avoid disruption as far as possible.

Reports about political shenanigans behind the scenes have also been circulating at the annual BIO Convention, which this year is taking place in San Diego. *(Also see "Midsummer Madness: EMA Headquarters Rumors Fly At BIO" - Pink Sheet, 20 Jun, 2017.)* One rumor is that Germany and France have agreed to back the EMA going to an eastern European country in return for splitting the EBA into two entities based in Frankfurt and Paris, although it is difficult to see how this would be done within a formal voting structure.

THE NEXT STEPS

The bidding procedure for the EMA is due to be formally adopted on the fringes of the June 22 meeting of the European Council (consisting of EU heads of government/state), where issues such as security, illegal immigration and globalization are on the agenda.

In a June 21 letter to the Council, its president, Donald Tusk, said that in the evening of the 22nd, UK prime minister Theresa May "will inform us on her intentions as regards the negotiations on the withdrawal" of the UK from the EU. "After dinner, I will invite the 27 leaders to stay for a brief update on the negotiations, and to endorse the procedure for the relocation of the UK-based agencies."

The member states will subsequently be invited to make their formal bids, which must be in by the end of July. *(Also see "July Deadline For EMA Relocation Bids; Member States Begin Scrutiny Of Proposed Hosting Criteria" - Pink Sheet, 24 May, 2017.)* "A substantial number of member states have already expressed interest to host the agencies," Dalli noted at the press conference. In fact, some 22 countries are understood to have done so, with notable exceptions being Slovenia and the three Baltic states.

Full details of the procedure will be published following the June 22 endorsement, a spokesperson for the European Council said. The final decision on the EMA's new location is scheduled to be taken in October.

From the editors of Scrip Regulatory Affairs. Published online June 21, 2017

Support For Continued EU Co-operation On Health Technology Assessment Is 'Overwhelming'

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There is strong support from a variety of stakeholders for continuing co-operation on health technology assessment across the EU after the current collaborative arrangements end in 2020, according to the European Commission. Respondents to a recent consultation run by the Commission also commented on what sort of governance mechanisms they would like to see in future and how fees for ongoing cooperation projects should be paid.

The Commission's Directorate General for Health and Food Safety ran the consultation, called "Strengthening of the EU cooperation on Health Technology Assessment," between November 2016 and January 2017.

It looked at whether HTA cooperation at EU level should continue beyond 2020 when the current EUnetHTA Joint Action 3 is

> "EU cooperation can enhance access to added value and affordable technologies in a timely manner and in the long run can also lead to savings, improving resilience and contributing to the sustainability of health systems"
> – EC consultation report

due to end. EUnetHTA (European Network for Health Technology Assessment) is a collaboration of 77 organizations across 29 countries that was created to establish "an effective and sustainable network for HTA across Europe." Joint Action 3, its most recent work program, aims to "define and implement a sustainable model for the scientific and technical cooperation on Health Technology Assessment (HTA) in Europe."

The responses to the consultation demonstrated "overwhelming support for sustainable cooperation on HTA at EU-level," said Vytenis Andriukaitis, Commissioner for Health and Food Safety. Some 87% of respondents said they support continued EU cooperation on HTA after 2020, he noted.

Andriukaitis added that he was keen to see a finalized proposal on how that co-operation might take shape before the end of the year. An impact assessment on strengthening EU cooperation on HTA beyond 2020 is planned for the fourth quarter of this year and will likely lead to an EU initiative.

The commission received 249 responses to the consultation from stakeholders, including pharmaceutical and medtech industries, HTA bodies, payers, patients, academia and healthcare providers. Industry was the biggest contributor, offering 52% of responses, according to a report on the consultation responses. Most were submitted by SMEs (46%) followed by "big commercial operators" (27%) and trade associations, including the European R&D-based industry body EFPIA (26%).

The report highlights a number of reasons among respondents for supporting continued cooperation. These include: ensuring a constant information exchange; increasing "synergies" between member states; streamlining HTA methodologies; increasing transparency and evidence-based decision making, and business predictability.

Meanwhile, some respondents noted that "EU cooperation can enhance access to added value and affordable technologies in a timely manner and in the long run can also lead to savings, improving resilience and contributing to the sustainability of health systems," said the report.

However, the types of joint activity called for depended on the stakeholder, according to the report. For example, industry, patients, academia and public administrations were generally in support of the development and use of joint tools (such as, templates and databases) and joint guidelines for clinical or economic assessments. And while most respondents saw joint clinical assessments on relative effectiveness as being useful to some extent, the medical technologies industry and SMEs were less interested in such activity.

Commentators also had their chance to give their opinions on how governance mechanisms for continued cooperation might take shape. Responses signaled a preference for an existing EU agency to take charge (66 out of 247 responses), rather than the European Commission (55 responses), a new EU agency (44), member state HTA bodies on a rotational basis (41) or some other body (41).

And with regard to funding mechanisms for future cooperation, the majority of responders (some 53 %) would like to see a mix of funding between contributions from the EU budget, member state contributions and industry fees. Industry respondents thought that funding should largely come from the EU budget but be supported by contributions from member states and a voluntary fee-for-service contributions from industry.

Respondents also stressed that EU cooperation on HTA should not put an additional financial burden on companies, in particular on SMEs, the report added.

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US FDA 'Medical Innovation Development Plan' Outlined By Gottlieb

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The US FDA will be releasing in the next six months a guidance on the clinical evaluation of targeted therapies for rare disease subsets as part of a broader "medical innovation development plan"designed to facilitate the development of breakthrough new treatments, agency Commissioner Scott Gottlieb announced.

Testifying June 20 before the Senate Appropriations Subcommittee on Agriculture, Rural Development, Food and Drug Administration and Related Agencies, Gottlieb said the "will address targeted drugs and how we can simplify the development of drugs targeted for rare disorders that are driven by genetic variations, and where diseases all have a similar genetic fingerprint, even if they have a slightly different clinical expression."

"One example is a cancer where a drug targets a particular molecular subset of cancer, regardless of where the tumor arises, Gottlieb said. "We'll clarify when we can give a broad approval to a drug in multiple different kinds of molecularly similar cancers, which are not particular to the tumor being in one specific tissue or organ."

The commissioner's announcement of the guidance comes nearly a month after **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab) became the first cancer treatment to be approved based on a common biomarker rather than the location where the tumor originated. *(Also see "Biomarker-Led Claim Is Small Step For Merck's Keytruda, Giant Leap For Cancer Indications" - Pink Sheet, 23 May, 2017.)*

A PD-1 inhibitor, Keytruda garnered accelerated approval May 23 for a supplemental indication for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). It is specifically indicated for colorectal cancer patients with these biomarkers that have completed earlier

FDA commissioner Scott Gottlieb

lines of treatment.

"Our new policy will describe when we will approach drug review less by when a disease is expressed and more by how it is driven by a common set of genetically driven factors," Gottlieb said.

During his confirmation process and at the start of his tenure as commissioner Gottlieb spent many of his public appearances discussing the facilitation of generic drugs to the marketplace. *(Also see "Brand Exclusivity 'Gaming' To Be Addressed At US FDA Meeting" - Pink Sheet, 25 May, 2017.)* While he did spend some time on generic drugs in a discussion on misuse of risk evaluation and mitigation strategies (REMS) and restricted distribution systems, he made new drugs front-and-center, offering some fresh insight on how a Gottlieb-led FDA will approach facilitating their development.

More broadly, Gottlieb said the agency will be updating several guidance documents on drug development techniques geared toward at aiding the discovery and development of targeted therapies. Such guidances, he said, would include those on "clinical trial enrichment strategies to improve efficiency, and adaptive trial designs to modernize the statistical tools we use to evaluate safety and effectiveness."

AN ORPHAN DRUG "SWAT TEAM"

One component of the medical innovation development plan that has already been put into place is an orphan drug "SWAT Team" to help eliminate the backlog of 200 orphan drug designation requests sitting at FDA, Gottlieb said.

The commissioner pledged that the agency would completely eliminate the backlog within 90 days with responses to requests, while also promising that "we will never again develop a backlog." Gottlieb further vowed that every orphan drug application will receive a response within 90 days of the request.

He additionally noted that FDA is implementing a "new, streamlined orphan designation review template."

The backlog may have been caused in part by the increasing popularity of orphan drugs by sponsors. *(Also see "Disease 'Subsetting' Not Driving Jump In Orphan Designations, US FDA Says" - Pink Sheet, 28 Nov, 2016.)*

CREATING DISTANCE FROM BUDGET, HEALTH CARE BILL

Sen. Jon Tester, D-Mont., pointed to a recent US Congressional Budget Office (CBO) score, which concluded that FDA would need additional resources beyond user fees to carry out all the programs envisioned in the Senate's user fee reauthorization bill, many of which are related to generic drugs. *(Also see "Generic Program Is Biggest Extra Item In Senate User Fee Reauthorization Bill" - Pink Sheet, 20 Jun, 2017.)*

Tester questioned how Gottlieb would implement these programs under President Trump's budget proposal if it were to be enacted.

The commissioner once again created

some distance between himself and the president's proposal, noting that he wasn't involved in the formulation of the budget, as he did before the House Appropriations subcommittee in May. *(Also see "Gottlieb Distances Himself From Trump's User-Fee Heavy Budget" - Pink Sheet, 25 May, 2017.)*

Gottlieb did, however, say that he "would have to obviously make it work if the budget would pass as it was proposed."

"These are challenging budgetary times, and we are going to have to figure out ways to do more with less," Gottlieb said.

"We have tried to allocate the reductions to places of lower priority. But in an agency where there is an important mission, and a lot of what we do is important, sometimes it is challenging to find those areas, and we try to do the best we can to identify them."

Sen. Jeff Merkley, D-Ore., who serves as ranking member of the subcommittee, also questioned whether Gottlieb was consulted by any of the 13 Republican senators working in closed-door proceedings on a Senate version of the American Health Care Act. Gottlieb responded he has had "no dialogue with any group working on legislation.

Merkely stressed his desire, as well as that of other Democrats, to have an open, transparent discussion on the health legislation. The issue of the legislative proceedings hijacked a recent Senate Committee on Health, Education, Labor and Pensions hearing that was supposed to be about drug pricing. *(Also see "Drug Pricing 'Deeper Dive' Planned By Senate Cmte. As Industry Avoids First Blood" - Pink Sheet, 14 Jun, 2017.)*

OPIOID PLAN FOCUS ON EDUCATION

Gottlieb also distanced himself from the health legislation proceedings when asked about the agency's plan to address the opioid epidemic.

Merkely raised concerns about the House-passed version of the American Health Care Act, which he said would cut "billions of dollars" for treatment of mental health and substance abuse disorders and cause millions of people to lose insurance.

"I have not focused a lot of attention on the various legislation moving through with regard to the Affordable Care Act," Gottlieb said. "I am very focused on what I am doing at FDA right now."

Gottlieb noted that the agency has established a steering committee at FDA composed of center directors and clinicians that is examining several aspects of the opioid crisis, including making sure that properly indicated patients receive opioids and they are prescribed for an appropriate duration, putting a framework in place for looking at risks in an illicit setting, and improving prescriber education. *(Also see "Opioid Policy At US FDA To Become 'More Forceful,' Gottlieb Says" - Pink Sheet, 23 May, 2017.)*

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Novo's Victoza CV Benefit Claim Could Be Narrowed With FDA Panel Vote

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Novo Nordisk AS's *Victoza* (liraglutide) appears on track to add cardiovascular benefit labeling following a US FDA advisory committee's endorsement June 20 but the supplemental indication could end up narrower than the sponsor would like.

The Endocrinologic and Metabolic Drugs Advisory Committee voted 17-2 that the results from the LEADER CV outcomes trial provided substantial evidence to establish that the GLP-1 receptor agonist reduced CV risk in patients with type 2 diabetes.

However, numerous panelists who voted in favor of a new indication balked at Novo's request for a broad claim encompassing both secondary and primary prevention.

Novo is seeking approval as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse CV events (MACE) in adults with type 2 diabetes and high CV risk. While the overall LEADER trial was positive, the results trended in the wrong direction for the subgroup of patients who did not have established CV or chronic kidney disease.

"I do feel strongly that they have not demonstrated benefit in the lower risk group," said James de Lemos, a cardiologist at University of Texas Southwestern Medical Center. He suggested labeling the drug for "cardiovascular risk reduction among individuals at high cardiovascular risk on the basis of prevalent clinical or subclinical cardiovascular disease or chronic kidney disease."

"I think it should have an indication for reduction of MACE in patients with established cardiovascular disease or with CKD," said Leslie Cho, a cardiologist at Cleveland Clinic. "I think the broader indication for high cardiovascular risk in which things like [left ventricular] dysfunction, microalbuminuria and some other things that were included … is a troubling aspect of this yes vote."

Those voting against approval said they could not reconcile the negative efficacy results in another subgroup – US patients.

"The indication asked for is as an adjunct to standard treatment in the US, for a US label," said Daniel Budnitz, director of the Medication Safety Program at the Centers for Disease Control and

Prevention. "If a subgroup analysis that looks at US residents versus the world isn't appropriate to do, then I don't know what subgroup analysis we should ever do."

Panelists generally said the LEADER study did not raise new concerns about the risks of thyroid cancer and pancreatic cancer but also did not put those concerns entirely to rest.

The application's user fee date is Aug. 25.

FDA has previously approved only one antidiabetic agent with a CV benefit claim – **Boehringer Ingelheim GMBH** and **Eli Lilly & Co.**'s SGLT2 inhibitor *Jardiance* (empagliflozin), which is indicated to reduce the risk of CV death in adults with diabetes and established CV disease. *(Also see "Jardiance's Cardiovascular Benefit Claim Bodes Well For Other Products Too" - Pink Sheet, 5 Dec, 2016.)*

DIFFERENT EFFICACY RESULTS FOR US PATIENTS

In the 9,340-patient LEADER trial, liraglutide demonstrated a statistically significant 13% reduced risk in the MACE composite endpoint and a 22% reduced risk in the CV mortality component. The other two MACE components, non-fatal myocardial infraction and nonfatal stroke, trended in favor of liraglutide but were not statistically significant.

FDA's briefing document for the meeting did not raise any red flags about the efficacy data but, rather, focused extensively on the non-CV safety data. *(Also see "Victoza's Non-Cardio Safety May Dominate At FDA Panel Review" - Pink Sheet, 17 Jun, 2017.)*

However, much of the advisory committee's debate centered on two efficacy issues that received little or no attention in FDA's briefing document – unfavorable results in the US subpopulation and individuals ages 60 years and older with CV risk factors but not established CV disease.

For both subgroups, the hazard ratio point estimates for MACE were above 1.0, which "could suggest possible inconsistency in the effect for MACE across these subgroups," FDA Clinical Reviewer Tania Andrea Condarco said. *(See table)*

Noting that the interaction p-value for both subgroups was below 0.05, Condarco said: "This is marginal evidence that the size of treatment effect may be different between these subgroups. However, there is no strong evidence that the direction of treatment effect was different."

The US accounted for 27% of the patients in LEADER. Condarco said the subgroup results were "worth noting because approval of a cardiovascular benefit indication would be based on the assumption that the overall trial results are applicable to the US patients and the US standard of care."

Novo suggested the unfavorable hazard ratio point estimate in the US subgroup resulted from a higher rate of permanent drug discontinuation, and consequently an overall lower exposure time to trial product, compared to non-US subjects. An on-treatment analysis of time to first MACE yielded hazard ratio estimates in the US consistent with that of the overall population, Novo said.

However, FDA is not yet ready to sign onto this theory.

"It is not clear to us that the applicant's selected analytical methods were the most appropriate way to address the question," Condarco said. "We are therefore not prepared at this time to endorse the concept that exposure can explain the US findings, if real."

Although some panelists said they were unsure why the US subgroup results were different, most agreed they should not override the overall positive findings from the study.

CV RISK FACTORS, BUT NO DISEASE

The second subgroup of focus – patients ages 60 years and older with CV risk factors – accounted for 19% of LEADER's randomized population but only about 10% of first MACE events.

The unfavorable point estimate in this group "is worth noting from a clinical standpoint because the applicant seeks an indication for both primary prevention and secondary cardiovascular disease prevention," Condarco said.

Cardiologist Marvin Konstam, Tufts University, said that while he did not think it was possible to draw any conclusions from the subgroup, "it's highly relevant to what the labeling's going to be."

LEADER Subgroup Efficacy Differences

CATEGORY	NUMBER OF PATIENTS	MACE HAZARD RATIO (95% CI)
Country		
Outside US	6,826	0.81 (0.71, 0.92)
US	2,514	1.03 (0.84, 1.25)
Cardiovascular History		
Established CVD or CKD and age ≥50 years	7,598	0.83 (0.74, 0.93)
CV risk factors and age ≥60 years	1,742	1.20 (0.86, 1.67)

Source: FDA and Novo Nordisk briefing documents and slides.

"I think the evidence resides in patients who have established cardiovascular or renal disease, mostly cardiovascular disease," Konstam said. "I think that's where the relevance of those groupings come in, not drawing a definitive conclusion."

"It seems completely inappropriate to me to offer an indication … to a group that is tiny and didn't demonstrate even a shred of benefit," de Lemos said, adding that there is plausibility for drugs that work differently in secondary and primary prevention.

"I think it's fairly clear cut that if there's an indication, it really has to be limited to the people in whom it was studied, which is secondary prevention," he said. "It was such a small subgroup of primary prevention."

NON-CV SAFETY REASSURING

Several panelists said the strength of the overall CV benefit data, coupled with low rates of safety events of interest, helped to assure them about liraglutide's benefit/risk profile.

"There's precious little evidence for medullary and thyroid cancer risk [in] a substantial size trial," said University of Florida oncologist Carmen Allegra.

As for pancreatic cancer, "although there seems to be potentially a numeric difference between the placebo and the treated group, the numbers are incredibly small," he said. In addition, most of the pancreatic cancers were diagnosed within one-and-a-half years of study enrollment, which would not suggest a causal relationship given the long latency period for such cancers, he said.

"Those two facts coupled together make me pretty comfortable that this agent isn't causing cancer, and I don't even believe it's accelerating the appearance of pancreatic cancer," Allegra said.

ADVISORY COMMITTEE VOTES

- Do the results of LEADER establish that use of liraglutide in patients with type 2 diabetes is not associated with unacceptably high cardiovascular risk?
  Y – 19, N – 0
- Does the LEADER trial provide the substantial evidence needed to establish that liraglutide 1.8 mg daily reduces cardiovascular risk in patients with T2DM?
  Y – 17 , N – 2

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Oral Contraceptive Switch Advocates Reject User Age As Approval Factor

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An application to allow OTC access to an oral contraceptive soon could reach FDA. Proponents already are pushing for its review to be based solely on a safety and efficacy analysis that leaves customer age out of the equation.

Groups such as the Oral Contraceptives Over-the-Counter Working Group want to make sure that age, the controversial element in FDA's decision on nonprescription sales of emergency contraceptives, does not resurface, even though a court ruling forced FDA to remove age restrictions from the emergency products.

Ibis Reproductive Health and **HRA Pharma SA** are close to submitting to FDA the results of work they began in December to prepare an application for an oral contraceptive switch, according to researchers with knowledge of the partnership's progress.

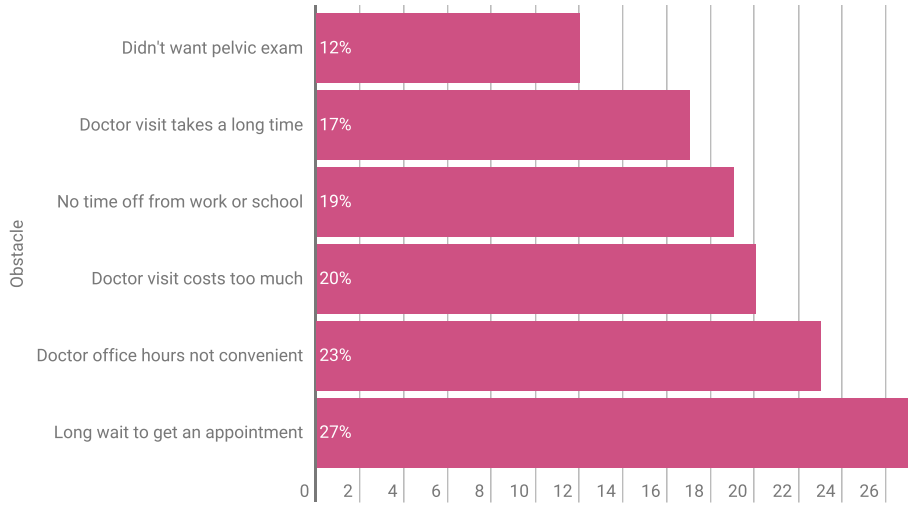
> Ibis Reproductive Health and HRA Pharma appear close to submitting to FDA the results of work they began in December to prepare an application for an OC switch.

Ibis, a women's health and reproductive rights advocacy group, says OTC sales are needed not only for convenient, lower-cost access to safe and effective drugs but also because insurance coverage for prescription products might be diminished. Proposals by President Trump and Republicans in Congress to repeal the Affordable Care Act and replace it with a new law would delete ACA's requirement that most insurance plans cover FDA-approved contraception, without copayments. Expanded exemptions to that requirement were already made by the US Supreme Court's "Hobby Lobby" decision, saying that certain kinds of employers cannot be required to provide contraceptive coverage that offends their religious beliefs. *(Also see "HHS Plan To Exempt Employers From Birth-Control Mandate Threatens IUD Sales" - Medtech Insight, 6 Jun, 2017.)*

"Given the many attacks on women's health and rights at the federal level, it is even more critical that we take proactive

Obstacles To Purchasing Rx Oral Contraceptives

Among 725 Women Who Used Or Wanted A Prescription Contraceptive



Women's Interest In OTC Oral Contraceptives

2,046
Nationally representative survey

62%
Supported OTC access to OCs

27%
Reported being likely to use OTC OC

- **59% of current OC users**
- **33% of women using a less effective method**
- **29% of women using no method**

Interest highest among younger women, living with partner, private or no insurance.

Source: Oral Contraceptive OTC Working Group, Dan Grossman, et al

HOW COMMON ARE CONTRAINDICATIONS?

Most prevalent with use of combination oral contraceptives:

- migraine with aura, 18%
- hypertension, 22%

Most prevalent with use of progestin-only oral contraceptives:

- medications for tuberculosis or seizures, 0.9%
- liver disease/cancer, 0.4%
- breast cancer, 0.3%

measures to expand contraceptive access," said Britt Wahlin, Cambridge, Mass.-based Ibis' vice president for development and public affairs.

In an email, Wahlin said Ibis and HRA's work "is moving ahead as planned," but declined to estimate when the partnership would file an NDA or whether representatives have had pre-application meetings with FDA.

Adolescents, she said, "will be part of the pivotal research that will be conducted and presented to the FDA as part of HRA's application for an OTC" progestin-only contraceptive.

"Oral contraceptives are safe for adolescents, and adolescents like all people should be able to access contraception if they wish to prevent pregnancy. … We expect the FDA to conduct a rigorous scientific review and make a decision based on the evidence," Wahlin added.

About a potential oral contraceptive switch, a spokesman for FDA's Center for Drug Evaluation and Research said patients' age is considered in the center's evaluation, but it could not "comment on the potential approval of a specific product."

CDER's drug application "approval decisions are based on review of numerous factors related to the potential for safe and effective use of the product, and age of the user is among the factors considered," the spokesman said.

'COMMUNITY … CONSENSUS' OF SUPPORT

FDA's decision based on the evidence should be obvious, says Susan Wood, the well-known advocate on these issues who is an associate professor in at George Washington University's Milken School of Public Health and director of the Jacobs Institute of Women's Health there.

"There's been a community of people looking at different aspects of this question and finally coming to a consensus, I think, that we should be bringing one if not multiple oral contraceptive products over the counter sometime in the foreseeable future," Wood said at a recent OTC drug industry conference.

"When you compare it to other over-the-counter medicines, I don't think it's

coming with any special risks," she added. Woods resigned from an FDA position a decade ago due to her objections about delays in approving OTC emergency contraceptive products.

"Women are interested in getting an oral contraceptive without a prescription," Wood says *(see charts)*.

Much of the community looking at OTC access to oral contraceptives are participants in or supporters of the Oral Contraceptives Over-the-Counter Working Group of reproductive health, rights and justice organizations, nonprofit research and advocacy groups, university-based researchers and clinicians launched more than decade ago.

The OC OTC Working Group currently lists dozens of medical groups and experts as supporters of its "statement of purpose" of "providing all women of reproductive age easier access to safe, effective, acceptable, and affordable contraceptives." (Ibis executive Wahlin is listed as a steering group member.)

In addition to the safety and efficacy of oral contraceptives, the OC-OTC Working Group has looked at potential health impacts when women do not consult a physician before using the products. The group also also tracks changes in states on lowering barriers to accessing the products.

Consumers and health care providers are concerned about not women not receiving screenings for contraindications; choosing a formulation; and out-of-pocket costs. Consumers also have questions about whether OTC access would prompt more teens into unprotected sex while doctors note a problem in losing opportunities to counsel women about long-acting reversible contraceptive methods.

"People do worry about this. This is why it took a discussion of probably 10 years or more, definitely more, talking about things that we needed to prove," Wood said at the Consumer Healthcare Products Association's OTC regulation conference in Rockville, Md.

With fewer and rarer contraindications than combination progestin and estrogen formulations, progestin-only products should be the first OTC oral contraceptives, the OC OTC Working Group recommends *(see box, p. 10)*.

Still, FDA will want proof of correct self-selection and actual use because progestin-only products must be used around the same time each to be effective.

"So, there are some concerns on making sure that women can use it correctly," Wood said.

One outcome that some opponents of an oral contraceptive switch predict, encouraging unprotected sex among teens, should not be a concern, Wood believes.

The OC OTC Working Group supports nonprescription status for an oral contraceptive without age restrictions and pharmacy-only sales, which were controversial elements of the first emergency contraceptive FDA approved for nonprescription distribution. Litigation by women's health advocacy groups eventually forced FDA to remove both types of limits to access. *(Also see "FDA Drops Access Restrictions On Generic OTC Emergency Contraceptives" - Pink Sheet, 5 Mar, 2014.)*

"We all know that there are very limited age restrictions on over-the-counter products. This was part of the battle of getting emergency contraceptives over the counter, a battle over the age restriction," Wood said.

Research shows daily oral contraceptive use does not produce that result among teens, and removing age restrictions for emergency contraceptive purchases – first lowering the minimum age from 18 to 17 before eliminating any restriction – also has not increased the behavior.

"It wasn't until 2013 that it's been available without an age restriction. My first comment always when noting that the age restriction was lifted in 2013, is that the sky did not fall," Wood said.

Eliminating age restrictions also made emergency contraceptives more accessible for other consumers. The change "lifted restrictions off older women from having to go to the pharmacy counter to buy the product," she said.

OTC sales of nicotine replacement products were approved by FDA with an age restriction of 18 and older, while some states have imposed the same restriction on nonprescription sales of cough remedies containing dextromethorphan.

Research by OC OTC Working Group members and other experts published in March in the Journal of Adolescent Health also recommends against age-restricting oral contraceptive sales.

The study noted National Survey of Family Growth population surveys suggest that with wider nonprescription access to emergency contraceptives, teens' use also increased from 8% in 2002 to 22% in 2011. Sexual behavior data from the surveys indicate no increase in the number of teens initiating sexual intercourse or reporting recent intercourse.

"The increase in use of EC that has followed reduced restrictions suggests that there is a need for improved contraceptive access for teens and that, when contraceptives are made easily available, adolescents will use them," the researchers said.

They also noted an "assumption often stated" by some physicians is that adolescents are less likely than older women to use oral contraceptives correctly. National Survey of Family Growth data from 2001 show similar "contraceptive failure rates" for females under 18 years old (13.8%), 18 to 19 (14%) and 20 to 24 (14.9%).

The NSFG data also "indicate that failure rates for condoms in these same age groups (25.8%, 27.5%, and 28.2%) are higher than those of OCs and also do not vary significantly by age among minors versus older adolescents and young adults," according to the Journal of Adolescent Health study.

From the editors of the Tan Sheet.
Published online June 22, 2017

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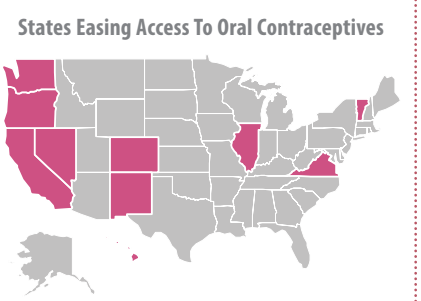
States Ease Access To Oral Contraceptives Despite Rx Requirement
http://bit.ly/2rWanLX



Pfizer's EPO Biosimilar Stalls In US On Hospira Compliance Woes

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Pfizer Inc. is working to resolve lingering compliance issues at a legacy **Hospira Inc.** manufacturing facility that have blocked its bid to bring the first biosimilar version of epoetin alfa (**Amgen Inc.**'s *Epogen*/**Johnson & Johnson**'s *Procrit*) to the US market.

On June 22, Pfizer announced receipt of an FDA complete response letter a day earlier for its epoetin alfa biosimilar (proposed trade name *Retacrit*). The regulatory action marks the second time FDA has declined to approve the 351(k) application that Pfizer inherited through its acquisition of Hospira in September 2015.

The current letter "relates to matters noted" in a Feb. 14 warning letter for a Hospira drug manufacturing facility in McPherson, KS, where the biosimilar was to be manufactured, Pfizer said.

The issues noted in the warning letter do not relate specifically to the manufacture of epoetin alfa," Pfizer said in a release. "No additional clinical data was requested in the CRL at this time to support a future approval."

In an interview with the Pink Sheet, Salomon Azoulay, senior vice president, chief medical officer and acting R&D head of Pfizer Essential Health, stressed that the regulatory delay did not involve issues with the biosimilar itself, and FDA's letter contains no mention about any deficiencies in the application.

It is "unfortunate that we have an issue at a manufacturing plant," Azoulay said, "but this issue is not directly related to EPO itself."

Nevertheless, the issue is one that will delay the biosimilar's approval for an unknown length of time.

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> "It is "unfortunate that we have an issue at a manufacturing plant," Pfizer's Azoulay said, "but this issue is not directly related to EPO itself."

EASY ODAC SUGGESTED CLEAR PATH AHEAD...

Just a month ago, Pfizer's epoetin biosimilar looked like it was headed for a quick approval despite a rocky first-cycle review.

Just a month after acquiring Hospira, Pfizer announced receipt of a complete response letter for the epoetin biosimilar application. Pfizer did not disclose details about that initial complete response letter except to say that further clinical trials likely would not be needed. *(Also see "Biosimilar Denied: Hospira's Retacrit Could Head Back To FDA In First Half 2016" - Pink Sheet, 27 Oct, 2015.)*

"The reasons Pfizer received a CRL from the FDA in 2015 are different from the recent CRL, which is related to manufacturing," a company spokeswoman said.

Although the company said it expected to resubmit the BLA in the first half of 2016, the submission was delayed until December 2016.

The application's second pass through FDA appeared to be going smoothly, at least based on the public advisory committee review.

On May 25, FDA's Oncologic Drugs Advisory Committee voted 14-1 that the totality of evidence supports licensure as a biosimilar for all indications on the Epogen labeling. *(Also see "Biosimilar Advisory Committees Getting Smoother, Even As Worries Stay The Same" - Pink Sheet, 25 May, 2017.)*

The panel's recommendation reinforced the views of FDA staff. In briefing documents released ahead of the meeting, FDA said there were no clinically meaningful differences between the Pfizer/Hospira product and Epogen, and the products were highly similar despite minor differences in clinically inactive components.

Those documents noted that FDA required Pfizer to change its manufacturing process after finding that the lots used for its clinical studies contained a higher erythropoietin content than US-licensed Epogen. Pfizer agreed to adjust the erythropoietin content to more closely match the reference product and to tighten the commercial product acceptance criteria. *(Also see "Hospira's Epogen Biosimilar Appears Poised For Quick Advisory Cmte. OK" - Pink Sheet, 23 May, 2017.)*

FDA's briefing document also noted good clinical practice violations at several trial sites but concluded these violations did not

alter the efficacy and safety conclusions from the studies.

Some advisory committee members were irked that postmarketing data for the biosimilar in Europe, where it is marketed as Retacrit, were not available for consideration. Even though the proposed US biosimilar product has same cell line and drug product formulation as EU-approved Retacrit, Pfizer did not bridge to it in its US biosimilar application. *(Also see "Pfizer Excludes EU Biosimilar Experience From US Epoetin Application" - Pink Sheet, 4 Jun, 2017.)*

... BUT TROUBLES LURKED AT MCPHERSON SITE

While much information about an application is disclosed publicly as part of the advisory committee process, details about the facilities at which products are going to be manufactured and any related compliance concerns are generally not brought to the external experts' attention.

However, FDA's concerns about the site at which Pfizer's biosimilar was to be manufactured were already well known.

On Feb. 14, the agency issued a warning letter stemming from an inspection of the McPherson, KS facility in May and June 2016. The warning letter cited the company's failure to adequately address the presence of visible particulates in products despite multiple complaint investigations, saying this represented "a significant loss of control" in the manufacturing process. *(Also see "Pfizer Suffered 'Significant Loss Of Control' At McPherson Plant, US FDA Warning Letter Says" - Pink Sheet, 28 Feb, 2017.)*

The letter also noted that the violations are similar to those cited in four other warning letters issued to Hospira over the past six years concerning other manufacturing sites.

"Until these violations are corrected, we may withhold approval of pending drug applications listing your facility," the warning letter states. "We may re-inspect to verify that you have completed your corrective actions. We may also refuse your requests for export certificates."

Several days after the warning letter's issuance, **Momenta Pharmaceuticals Inc.** announced that approval of its **Sandoz Inc.**-partnered ANDA for *Glatopa* (glatiramer) 40 mg, a generic of **Teva Pharmaceutical Industries Ltd.**'s multiple sclerosis drug *Copaxone*, was likely to be delayed by the compliance issues at the McPherson plant, where the product was to be manufactured. *(Also see "Pfizer Warning Letter Trips Up Sandoz/Momenta's Expected Glatopa Launch" - Pink Sheet, 23 Feb, 2017.)*

> "Until these violations are corrected, we may withhold approval of pending drug applications listing your facility." – FDA's Feb. 14 warning letter

Meanwhile, quality problems at the Hospira business also have led to shortages and recalls of critical drugs.

Pfizer attributes ongoing shortages of five injectable drugs to manufacturing, distribution and third-party delays. The products – sodium bicarbonate, dextrose 50%, epinephrine, calcium chloride and atropine sulfate – all have roles in emergency medicine.

Hospira also is recalling 42 lots of one of the shortage drugs, 8.4% sodium bicarbonate injection 50 ml vials, due to concerns about possible microbiological contamination.

PREPARING FOR FACILITY RE-INSPECTION

Pfizer's epoetin biosimilar now becomes the second new product known to have fallen victim to the McPherson site's compliance troubles.

In its release, Pfizer said it submitted a corrective and preventative action plan to FDA in March and has been working diligently to address the items raised in the warning letter. "Pfizer provides regular updates to FDA on the status of its action plan and remains dedicated to addressing all of FDA's concerns with the McPherson, KS site," the company said.

Azoulay said the company is "taking every corrective action" and "working very closely with the FDA" to get ready for a re-inspection of the facility. However, he could not provide a timeline for when the re-inspection would take place or when the biosimilar might be approved.

When asked whether the McPherson issues have delayed approval of any other Pfizer products, Azoulay said "not at this time." The compliance issues have had not impacted Pfizer's currently marketed products, he said.

When asked whether Pfizer has considered moving the epoetin biosimilar's manufacturing to another facility, Azoulay said the company is focused on addressing the agency's concerns about the McPherson plant.

Despite the regulatory delays in getting its version of epoetin to market, Pfizer reaffirmed its commitment to the biosimilars market in general as a means for increasing patient access to important medicines, and to biosimilar epoetin in particular.

"The company is committed to making this important treatment option available to patients and physicians as quickly as possible," Pfizer said in its release.

In addition to epoetin alfa, the company's website lists five other biosimilars in registration or Phase III development that reference the following products: **AbbVie Inc.**'s *Humira* (adalimumab), **Genentech Inc.**'s *Avastin* (bevacizumab) and *Herceptin* (trastuzumab), **Janssen Biotech Inc.**'s *Remicade* (infliximab) and Genentech and **Biogen**'s *Rituxan* (rituximab).

Pfizer markets **Celltrion Inc.**'s *Inflectra* (infliximab-dyyb), a biosimilar to Remicade, in the US and overseas. The biosimilars Retacrit (epoetin zeta) and *Nivestim* (filgrastim), which references Amgen's *Neupogen*, are marketed overseas.

Bowman Cox contributed to this story.
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WHO Consults On Standardized Approach To Verifying Good Practices At Foreign Sites

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WHO's proposed "desk assessment pathway" could result in foreign drug manufacturers and clinical trial sites facing fewer inspections because NRAs would be able to rely on evidence from other regulatory authorities.

The World Health Organization is inviting stakeholder feedback on a standardized procedure that national regulatory authorities (NRAs) can follow to carry out a desktop review of inspection reports issued by trusted, competent regulatory bodies in order to verify compliance with good practices concerning manufacturing, quality control and conduct of clinical trials of medicinal products in foreign countries.

The WHO's proposed "desk assessment pathway" is outlined in a draft guideline which, when finalized, could result in foreign drug manufacturers and clinical trial sites facing fewer inspections because NRAs would be able to rely on "authentic and reliable documentary evidence from other regulatory authorities," the WHO said.

Specifically, the guideline applies to manufacturers of finished pharmaceutical products and active pharmaceutical ingredients, clinical trial sites and clinical research organizations, and quality control laboratories subjected to good practice (GxP) inspections in foreign countries. The procedure can also be used by NRAs for the assessment of national sites and to define their own inspection programs.

The guideline outlines a set of essential information and documents that drug manufacturers, quality control laboratories and clinical trial sponsors should make available to NRAs to enable them to undertake desk assessment in relation to the most relevant GxPs, namely manufacturing (GMP), quality control (GLP) and clinical trials (GCP). It clarifies, however, that the desk assessment process does not preclude an on-site inspection in cases where the outcome of the assessment shows non-compliance with stipulated practices.

While the desk assessment process to verify compliance with GMP and GCP has been used by the WHO's Prequalification Team, the European Medicines Agency and Australia's Therapeutic Goods Administration for some years, the WHO notes that "for others it is an emerging consideration." The organization explains that it decided to develop formal guidance on this front following a request from national medicines regulatory authorities who attended a training symposium on collaborative registration procedures in Kenya inSeptember 2016.

While the WHO's guideline has general geographical applicability, it is more relevant to regulatory authorities in low- and middle-income countries where it can help support ongoing harmonization initiatives and help make optimum use of limited resources. The guideline clarifies that desk assessment procedures cannot be applied to sites that have failed GxP inspections, and that the NRA is ultimately responsible for deciding whether it is appropriate to perform a desk review.

The desk assessment process depends on several factors, such as whether the facility was previously inspected by one of the competent NRAs, or a member of the international Pharmaceutical Inspection Co-operation Scheme (PIC/S) or under the WHO's prequalification scheme, and whether any agreements are in place between the NRA and the foreign country, such as for mutual recognition, cooperation or memoranda of understanding.

The guideline lists specific documents and certificates for each type of facility – manufacturer of sterile or non-sterile FPPs, APIs and biotech; outsourced testing laboratory; and CROs – that must be submitted as evidence to enable desk review of applications in the following cases:

- Where a mutual recognition agreement exists.
- Where a cooperation agreement or an MoU exists or the facility has been inspected by a PIC/S member or a stringent regulatory authority, or under the WHO prequalification scheme
- Where no agreements are in place and the facility has not been inspected by a trusted regulator.

It also has annexes on model report formats for desk assessment of FPPs and API manufacturers, quality control laboratories, and CROs/clinical trial sites.

Comments on the draft guideline will be accepted until July 15.

From the editors of Scrip Regulatory Affairs. Published online June 19, 2017

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Regulators Accepting Predictive Stability Data In Lieu of Long-Term Studies

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The pharmaceutical industry is getting more comfortable with using predictive stability models to accelerate stability testing for new drug products, and this testing is being used to support a wide range of applications. These models are increasingly being used to obtain approval for new drugs, though their use in supporting post-approval changes remains limited, concludes an industry benchmarking survey.

Brian Regler, associate principal scientist of **Merck & Co. Inc.**, said the survey shows that predictive stability modeling "is gaining traction and is being used more frequently." He further noted that "in the clinical space, regulators are accepting it in terms of filing, and acceptance is very, very good. Hopefully this will spill over to the commercial space."

The survey was sponsored by a working group within the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ). The aim of the study was to gauge the regulatory acceptance of predictive stability studies.

Regler discussed the status of predictive stability programs in the industry as well as the results of a recent survey on predictive stability at the Drug Industry Association's recent CMC workshop in Rockville, Md.

The International Council for Harmonization's Q1A(R2) guideline recommends that 12 months of long-term stability data should be available at the time of filing. The guideline sets 25 degrees Celsius and 60% relative humidity for the US, the EU and Japan for long-term stability testing conditions. The guideline does not traditionally allow for such data to be collected over a compressed period or permit extrapolation of stability data with respect to changes in humidity and packaging. Yet the survey shows that some health authorities are accepting the results of predictive stability data in lieu of long-term stability data.

Regler said that predictive stability studies can be performed during clinical development to support new drug applications and to support post-approval changes by using models to predict stability in a compressed period. These studies extrapolate kinetic models from short term timepoints to predict long-term stability. The packaging must be integrated to test container humidity. These studies generally run for one or two months.

These studies are also commonly performed to measure loss of assay and the formation of degradation products, and there is a lot of effort underway on using these models to predict dissolution.

Regler said that 20 pharmaceutical companies are using one of three predictive stability models for these applications:

- Accelerated Stability Assessment Program: This model was developed in early 2000 by former **Pfizer Inc.** research fellow Ken Waterman. This approach uses a humidity-corrected Arrhenius equation to extrapolate long-term data from stability data collected over a period of three weeks to set expiration or shelf life.
- Accelerated Stability Modeling: This is the in-house approach used by **GlaxoSmithKline PLC**. Under this model, drug products are exposed to extreme storage conditions such as temperature and humidity for short periods, typically 14 days, simulating what would happen over longer periods of shelf life.
- Predictive Statistical Stability: This is the in-house method used by Merck. Under this model, stability conditions are built around the intended long-term storage environment using response surface methodology. Data is fit to a multilinear regression with effects determined by standard statistical practice, and predictions are run after four and eight weeks of storage.

Regler said that these three models are similar in that they all measure temperature, time points and humidity.

He said that to ensure that these studies are effective, it is

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Merck's Brian Regler said an industry survey shows that predictive stability modeling "is gaining traction and is being used more frequently."

important to model all degradation products and not just focus on those degradants with the highest signals in determining if they pose a risk for failure on stability. "In your study, if you see there are 11 degradation products, don't just look at those with the highest values. You want to run all of the degradants to understand that maybe it is one or two that does not give you the signal."

It is also important to understand that the accelerated technique does not accelerate all reactions equally and that "higher powered protocols and longer studies may be needed for some products as development advances."

IQ SURVEY FOCUSED ON PREDICTIVE STABILITY USE

To get a sense of the extent to which these studies are being used in regulatory filings, a working group within IQ decided to survey its members. The working group consists of representatives from 11 pharmaceutical manufacturers.

The IQ risk-based predictive stability working group regulatory sub-team consisted of representatives from **AbbVie Inc.**, Eli Lilly & Co.,Genentech Inc.,Johnson & Johnson,Boehringer Ingelheim GMBH,Biogen Inc.,Bristol-Myers Squibb Co.,**Pfizer Inc.**, **GlaxoSmithKline PLC**, **AstraZeneca PLC** and Merck.

According to a report, IQ members would like to accomplish two goals from the survey: to harmonize the level of detail and publish a template that could be used for regulatory filings for predictive stability studies. Another goal is to lobby ICH to update the ICH Q1A with a question-and-answer document informing manufacturers about the use of risk-based stability approaches.

The 56-question survey was distributed to IQ analytical leadership of 33 companies; 19 companies responded. All the respondents made new drug products and some of them also made generics.

MOST HAVE USED PREDICTIVE STABILITY

Of the 19 respondents, 16 (84%) reported using predictive stability studies. Of the total, most manufacture small molecule drugs. Nine of the respondents report using ASAP and two are using in-house predictive models.

The survey also found that manufacturers are using predictive stability models for a wide variety of applications. For example, 90% of survey respondents are using them for formulation screening, 90% for selecting the packaging, 80% for predicting shelf life, 65% for demonstrating equivalence, and 12% for site-specific stability testing.

Five manufacturers have submitted NDAs that rely on predictive stability studies, while two have used such studies to support post-approval changes. Only three companies gave further details on using these approaches in getting NDAs approved but reported that "successful applications worldwide were achieved."

And only one company gave details of using predictive stability in getting a post-approval modification accepted for a packaging change.

From the editors of the Gold Sheet. Published online June 20, 2017

Yet Another Delay For Landmark EU Clinical Trial Rules – Now To 2019

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Technical difficulties experienced with developing the IT systems needed for the forthcoming EU clinical trial portal and database have made it impossible for the new Clinical Trial Regulation to come into effect in October 2018 as previously planned.

Because the portal and data need to be up and running before the CTR can take effect, the new legislation will now not become applicable until 2019, the European Medicines Agency revealed today.

This is not the first time the schedule has slipped for the portal and database, which the EMA describes as "the most ambitious IT system required by the EU legislation in the last decade." Earlier

ABOUT THE CLINICAL TRIAL REGULATION

The CTR (EU No. 536/2014) was adopted and entered into force in 2014, but the portal and database need to be built before the regulation can take effect.
The new system under the CTR will provide a single portal for the submission and maintenance of clinical trial applications and authorizations, and support coordinated assessment and supervision. The portal and database will also serve as the source of public information on the full lifecycle of all clinical trials conducted in the EU, from their initial review up to the publication of their results.

According to the EMA, the CTR will harmonize the electronic submission and assessment process for clinical trials conducted in multiple EU member states, and improve collaboration, information-sharing and decision-making between and within member states. It will increase transparency of information on clinical trials and introduce the highest standards of safety for all participants in EU clinical trials.

predictions suggested kick-off dates of mid- or late 2016, and then late 2017. The previous 2018 go-live date had been adopted in December 2015. *(Also see "Elusive EU Clinical Trial Rules Slip Again – Now To Late 2018" - Pink Sheet, 30 Dec, 2015.)*

The new IT system "involves a complete EU-wide system to be used for clinical trial applications, urgent safety measures and other notifications to regulators before, during and after the conduct of clinical trials," the EMA said. Thousands of people are expected to use the new system once it goes live. The agency said its priority "is to ensure that a high quality and functional system is delivered to the EU regulatory network and its stakeholders."

The EMA learnt about the IT technical difficulties during its management board meeting on 14-15 June. "The Board was informed about the mitigation measures taken and the revised plan from the developer," it said, adding that it was working closely with the IT service provider "to ensure that corrective measures are implemented."

The agency now plans to provide an update at its next management board meeting in October this year, "where a new delivery time frame will be discussed once progress with development has been confirmed."

IMPACT ON TRAINING

The latest delay will also impact the EMA's schedule for training drug sponsors and European authorities in how to use the portal and database. The agency had previously forecast that training would become available during the second half of 2017 for the version of the system that had been built at that point. *(Also see "Training For 'Huge' EU Clinical Trials Portal And Database On Track For 2017" - Pink Sheet, 6 Jan, 2017.)*

"Training is linked to the stages of development of the system and will be re-planned alongside the revised time frame," a spokesperson for the EMA told the *Pink Sheet*. "We will be looking at means of increasing the availability of information on the system as it develops, so that a wider range of stakeholders can get familiar with the system," the spokesperson said.

Clinical trial sponsors and regulatory authorities will need to learn such things as how to register to use the new system, manage their user access to a clinical trial, and work in their designated workspaces using the new tools and capabilities provided.

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

FDA's NDA And BLA Approvals: Cotempla XR-ODT, Baxdela, Mydayis

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				
Neos	*Cotempla XR-ODT* (methylphenidate)	Extended-release orally-disintegrating tablet formulation of the stimulant to treat attention deficit hyperactivity disorder (ADHD) in patients ages 6 to 17 years of age.	S, 3	6/19/2017
Melinta	*Baxdela* (delafloxacin)	Antibiotic in tablet and injection formulations to treat acute bacterial skin and skin structure infections (ABSSSI).	P, 1	6/29/2017
Shire	*Mydayis* (mixed salts of single-entity amphetamine)	Extended-release once-daily formulation of the stimulant to treat attention deficit hyperactivity disorder in patients 13 years and older.	S, 3	6/20/2017
New Biologicals				
Roche (Genentech)	*Rituxan Hycela* (hyaluronidase /ritubimab)	Subcutaneous self-injection of the CD20-direct cytolytic antibody and endoglycosidase,to treat adults with follicular lymphoma, diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL).		6/22/2017
CSL Behring	*Haegarda* (C1 Esterase Inhibitor Subcutaneous (Human))	Routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients.		6/22/2017

KEY TO ABBREVIATIONS	
Review Classifications	**NDA Chemical Types**
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

Liability Win For Industry As US Supreme Court Curtails Forum-Shopping

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The US Supreme Court handed the biopharma industry a big win in an important forum-shopping case on June 19 by limiting where plaintiffs can bring mass tort product liability lawsuits. In an 8-1 decision, the high court ruled that state courts cannot exercise specific jurisdiction over mass tort claims brought by out-of-state residents.

Under the decision, plaintiffs may only sue in the state where they live and suffered the alleged injuries, or the state in which the defendant company is incorporated or headquartered.

In so ruling, the justices reversed a California Supreme Court decision allowing a mass tort lawsuit brought primarily by out-of-state plaintiffs to proceed against **Bristol-Myers Squibb Co.** for claims related to the use of the platelet inhibitor *Plavix* (clopidogrel).

Writing for the majority in Bristol-Myers Squibb v. Superior Court of California, San Francisco County, Justice Samuel Alito said: "The relevant plaintiffs are not California residents and do not claim to have suffered harm in that state. In addition … all conduct giving rise to the nonresidents' claims occurred elsewhere. It follows that the California courts cannot claim specific jurisdiction."

Justice Sonia Sotomayor was the lone dissenting vote, warning that the majority's decision would have "substantial" consequences by making it considerably harder for individuals to sue large corporations for a nationwide course of wrongdoing.

"The majority's rule will make it difficult to aggregate the claims of plaintiffs across the country whose claims may be worth little alone," Sotomayor said. "It will make it impossible to bring a nationwide mass action in state court against defendants who are 'at home' in different states. And it will result in piecemeal litigation and the bifurcation of claims."

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> "We are hopeful that this decision will provide litigants more certainty regarding where lawsuits can be heard." – Bristol-Myers Squibb and Sanofi

LAWYER: MASS TORTS WILL LOOK DIFFERENT

The decision means that "mass torts in biopharma and everywhere else are going to look considerably different from now on," said James Beck, a senior life sciences policy analyst at Reed Smith who represents drug and device companies.

"Plaintiffs have sued wherever they wanted to, wherever they thought they could get the best result. They can't do that anymore. They can't bring every suit in California or in Philadelphia," Beck said in an interview. "The days of having tens of thousands of plaintiffs in one state court without regard to where the plaintiffs are from are over."

"Plaintiffs' lawyers constantly seek to consolidate national lawsuits in friendly forums," said Richard Samp, chief counsel of the Washington Legal Foundation, which filed an amicus brief in the case.

"Today's Supreme Court decision should halt that practice. It makes clear that a plaintiff may not sue a corporate defendant in a state unless his claims arise in that state or else it is the corporation's home state."

In a statement, BMS and its Plavix commercial partner, **Sanofi**, said they were pleased with the high court's decision. "We are hopeful that this decision will provide litigants more certainty regarding where lawsuits can be heard," the companies said. "At its core, this decision was about basic principles of federalism and fairness in our legal system, and our legal team was deeply proud to be part of the process."

REJECTING A SLIDING SCALE APPROACH TO JURISDICTION

The decision sprang from eight separate complaints filed in California Superior Court by 678 plaintiffs who alleged Plavix damaged their health. Eighty-six of the plaintiffs were California residents and 592 were from 33 other states. All complaints asserted 13 claims under California law, including prod-

ucts liability, negligent misrepresentation and misleading advertising.

BMS, which is incorporated in Delaware and headquartered in New York, sought dismissal of the nonresident plaintiffs' claims for lack of personal jurisdiction. The California Superior Court in San Francisco denied the motion, concluding that California courts had general jurisdiction over the company because it engaged in extensive activities in the state.

On appeal, the California Supreme Court concluded that under a US Supreme Court decision in 2014, general jurisdiction was lacking.

However, the majority concluded that specific jurisdiction existed for the nonresidents' claims against BMS. The majority adopted a "sliding scale approach to specific jurisdiction" and concluded that BMS' extensive contacts with California permitted the exercise of jurisdiction. Also weighing in favor of jurisdiction was the similarity between the claims of the California residents and nonresidents, the state's high court said.

BMS appealed to the US Supreme Court, which granted review and heard oral arguments on April 25. *(Also see "Plavix's Day In Supreme Court: Is California Playing Fair On Product Liability?" - Pink Sheet, 25 Apr, 2017.)*

In his majority opinion, Alito discussed the two types of personal jurisdiction recognized by the Supreme Court: general jurisdiction, which is tied to the state in which the defendant is incorporated or headquartered, and specific jurisdiction.

"Our settled principles regarding specific jurisdiction control this case," Alito said. "In order for a court to exercise specific jurisdiction over a claim, there must be an 'affiliation between the forum and the underlying controversy, principally, [an] activity or an occurrence that takes place in the forum state.'" When no such connection exists, specific jurisdiction is lacking "regardless of the extent of a defendant's unconnected activities in the state."

The California high court's sliding scale approach is difficult to square with US Supreme Court precedent, Alito said.

"Under the California approach, the strength of the requisite connection between the forum and the specific claims at issue is relaxed if the defendant has extensive forum contacts that are unrelated to those claims," the opinion states. "Our cases provide no support for this approach, which resembles a loose and spurious form of general jurisdiction. For specific jurisdiction, a defendant's general connections with the forum are not enough."

> The majority "hands one more tool to corporate defendants determined to prevent the aggregation of individual claims, and forces injured plaintiffs to bear the burden of bringing suit in what will often be far flung jurisdictions." – Justice Sotomayor

The mere fact that the resident plaintiffs, like the out-of-state plaintiffs, were prescribed, obtained and ingested Plavix in California, and allegedly sustained the same injuries, does not allow the state to assert specific jurisdiction over the nonresidents' claims, Alito wrote.

In addition, the presence of BMS research facilities in California are not relevant to the question of specific jurisdiction. "What is needed – and what is missing here – is a connection between the forum and the specific claims at issue," the opinion states.

Alito also rejected what he called the plaintiffs' "last ditch contention" that BMS' decision to contract with **McKesson Corp.**, a California company, to distribute Plavix nationwide provided a sufficient basis for personal jurisdiction. "The bare fact that BMS contracted with a California distributor is not enough to establish personal jurisdiction in the state."

NO 'PARADE OF HORRIBLES'

The court's decision does not leave the out-of-state plaintiffs without a remedy, the majority said.

"Our straightforward application in this case of settled principles of personal jurisdiction will not result in the parade of horribles that respondents conjure up," the opinion states. "Our decision does not prevent the California and out-of-state plaintiffs from joining together in a consolidated action in the states that have general jurisdiction over BMS. BMS concedes that such suits could be brought in either New York or Delaware."

"Alternatively, the plaintiffs who are residents of a particular state – for example, the 92 plaintiffs from Texas and the 71 from Ohio – could probably sue together in their home states."

"In addition, since our decision concerns the due process limits on the exercise of specific jurisdiction by a state, we leave open the question whether the Fifth Amendment imposes the same restrictions on the exercise of personal jurisdiction by a federal court," the majority said.

DISAGREEMENT OVER WHAT IS FAIR

In a dissent that was almost as long as the majority opinion, Sotomayor noted that a core concern in the Supreme Court's personal jurisdiction caselaw is fairness. "There is nothing unfair about subjecting a massive corporation to suit in a state for a nationwide course of conduct that injures both forum residents and nonresidents alike," she said.

Sotomayor asserted that in this case, the three conditions established in Supreme Court caselaw for exercising specific jurisdiction over a nonresident defendant have been met.

First, BMS purposely availed itself of the privilege of conducting activities in California, she said.

Second, the plaintiffs' claims relate to BMS' conduct in the state, Sotomayor said, because they "concern conduct materially identical to acts the company took in California: its marketing and distribution of Plavix, which it undertook on a nationwide basis in all 50 states."

"That respondents were allegedly injured by this nationwide course of conduct in Indiana, Oklahoma, and Texas, and

not California, does not mean that their claims do not 'relate to' the advertising and distribution efforts that Bristol-Myers undertook in that state. All of the plaintiffs – residents and nonresidents alike – allege that they were injured by the same essential acts. Our cases require no connection more direct than that."

As for the third factor, "there is no serious doubt that the exercise of jurisdiction over the nonresidents' claim is reasonable," Sotomayor said, asserting that litigating the nonresidents' claims in separate suits in multiple states "would prove far more burdensome."

The majority decision would eliminate nationwide mass tort actions in any state other than those in which a defendant is based, the dissenting justice said. "Such a rule hands one more tool to corporate defendants determined to prevent the aggregation of individual claims, and forces injured plaintiffs to bear the burden of bringing suit in what will often be far flung jurisdictions."

MORE CASES, BUT FEWER 'WEEDS'

Reed Smith's Beck acknowledged that "more smaller mass torts" might result from the Supreme Court's decision. However, he said he favors anything that reduces the size of such cases because the problem with mass torts is they "allow very weak cases to hide in the weeds."

"I think there will be some lawn mowing of mass torts," he said.

In a post on the Drug and Device Law Blog, Beck pointed to another implication of the majority's ruling: "It affects available venues for a large number of federal causes of action."

Under the general federal venue statute, the scope of personal jurisdiction recognized by the Supreme Court in the Plavix case "subject to the court's final caveat … about federal personal jurisdiction[,] also becomes the template for the permissible venue choices available to federal plaintiffs bringing suit under any federal statute that does not contain its own statute-specific venue provisions," Beck wrote.

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OTC Sleep Aid Sales Snooze As Consumers Wake Up To Alternatives

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Sales growth for OTC drugs indicated as sleep aids has slowed as competition grows from natural products and other alternatives and as pharma firms curb advertising for their brands, says market research firm Kline & Co.

Kline's Nonprescription Drugs USA study, an analysis of the nonprescription industry's 2016 performance – including key trends, developments and new product activity – notes sales of OTC sleep aids by manufacturers grew 3.4% to $244m in 2016.

SLEEP GADGETS DEBUT

Sales of sleep technology products also are growing, especially among millennials, said Mahecha. The items include monitors, digital apps and other devices that incorporate light, sound and chill therapy to help users fall and stay asleep.

The impact of sleep aid devices and apps is yet to be determined, as many consumers still prefer taking an oral product and also are put off by the high price of the devices, Mahecha said.

Introductions in wearable sleep devices in 2016 included *Misfit Ray Sleep Monitor*, a wristband that tracks sleep duration and quality in addition to calories burned from walking, and the *Pzizz* sound app, which helps users fall asleep faster and tracks and records their sleep.

However, "after seeing significant growth rates ranging from 50% to 15% per year in the recent past, the market for OTC sleeping aids, which contain diphenhydramine or other monograph ingredients, is still growing, but at a much slower pace," Kline noted in a June 12 blog post on the study scheduled for release later in 2017.

Diphenhydramine-containing OTCs *ZzzQuil* from **Procter & Gamble Co.**, *Unisom* from **Sanofi**US subsidiary**Chattem Inc.** and from private labelers aids posted growth, but sales of other drugs in the category with the same ingredient, including **Prestige Brands Holdings Inc.***Sominex* and **Johnson & Johnson Consumer Inc.**'s *Simply Sleep,* were flat or down in 2016, Kline noted.

According to Kline figures from 2015, single-ingredient OTC drugs accounted for 81.7% of the total consumer health sleep aid market with sales of $236m, and natural products made up 18.3% of sales, $53m. Kline did not provide a break-down of the market for 2016.

Market research firm IRI data show that across the overall category of OTC and alternative sleep aids, sales of tablets and other solid dose products are growing faster than sales of liquid products. As with most consumer health care categories, private label sales lead the solid-dose category (*see chart, p. 22*).

60% CONSUMERS ARE TARGET MARKET

The number of consumers who have trouble sleeping or staying asleep continues to exceed the number who use OTC sleeping aids, "leaving this market ripe for more growth," according to Kline's study.

In an interview, analyst Laura Mahecha noted consumers' energy drink consumption as contributors to the

growing prevalence of sleeplessness. There's also increased neural stimulation from computer use.

"The younger generation are on screens so much, I think they might have more sleep problems," said Mahecha, an independent consultant for Kline in the health care, consumer product and industrial and institutional markets.

As much as 43% of US adults don't sleep well regularly and as much as 60% experience sleep disruption every night. However, "60% of the population are not buying these particular products," she said.

Consumers prefer to treat sleeping problems with natural options, such as chamomile tea or melatonin or valerian supplements, that they know are not habit-forming and will not cause grogginess after use. "A lot of people are afraid of taking sleep aids … and many don't see drugs as a solution to their problem," said Mahecha.

Melatonin-containing supplement brands include **Mylan NV**'s *MidNite* and **Pfizer Inc.**'s *Emergen-Zzz*; brands offering valerian supplements include Naturel Bounty Co.'s *Puritan's Pride* and **Pure Encapsulations Inc.**'s *Best Rest Formula*.

Mahecha added natural ingredients also are more practical for people with problems staying asleep. Most OTC drug sleep aids require a full eight hours of sleep to avoid the groggy effect the next day.

"If you wake up at 3 a.m. and can't fall back to sleep, you don't want to take a drug that's going to make you sleep through your alarm," she said.

When consumers turn to OTC drugs, they often look at pain relievers also formulated with a sleep aid, such as **Johnson & Johnson**'s *Tylenol PM* and **Pfizer Consumer Health Care Group**'s *Advil PM*.

Kline also notes the potential OTC switch of Takeda Pharmaceuticals USA Inc.'s *Rozerem* (ramelteon) in its "Rx-to-OTC Switch Forecasts USA: Next Frontier" report coming in the fourth quarter of this year.

Kline didn't provide details on a potential OTC market for the drug, which goes off patent in 2019, it previously identified as a good switch candidate, partly because it works with users' sleep-wake cycle and does not impact brain function like Rx drugs *Ambien* (zolpidem tartrate) and *Lunesta* (eszopiclone). *(Also see "Merck Silence On OTC Singulair Speaks Volumes On Switch Outlook" - Pink Sheet, 11 Dec, 2015.)*

Procter & Gamble's ZzzQuil brand showed sales growth in 2016 even as alternative products cut into OTC drug sleep aid sales.

Pfizer's Emergen-Zzz brand is among the melatonin-containing supplements competing in the consumer health sleep aid space.

Consumers may favor natural alternatives to avoid the grogginess that can result from OTC sleep aids.

ADVERTISING OFF, TOO

Despite competition from naturals and alternatives, OTC sleep aid advertising has not increased, a factor in the sales slump, says Mahecha.

One diphenhydramine OTC brand, Randob Laboratories Ltd.'s *Dormin*, has a 2017 ad campaign. Randob is promoting mass market distribution of its product available in independent pharmacies since 1950.

Dormin is ranked No. 3 in independent pharmacies and also is available through Amazon, the firm says. New retail customers for the brand include Bed, Bath & Beyond Inc. and Harris Teeter LLC, he said.

Cornwall, N.Y.-based Randob is expanding Dormin to food and mass merchandise channels because a second generation of family ownership re-invested in the brand, said President Jim Creagan.

"With strategic retail partners and marketing/advertising support for those channels, we want to ensure that Dormin is trusted for another 50 years," Creagan said in an email.

The expansion is supported with advertising including a humorous national TV campaign featuring a man struggling to stay awake and Facebook social marketing that includes the *Sleep Soundly Giveaway* sweepstakes for a $200 gift card for Bed, Bath & Beyond.

"The brand is taking a more novel, lifestyle approach with humor, using content targeting various segments (from millennials to the mature population based on message/targeting), and even tagging into current social news," said Creagan.

He added that Randob does not sense pressure from natural product competitors. Dormin works more quickly than natural sleep aids and allows for a full night's rest while many naturals aid in falling but not staying asleep.

"Natural sleep-aids are certainly a growing segment, but we do not view them as a threat," Creagan said.

From the editors of the Tan Sheet. Published online June 20, 2017

ZzzQuil Top Brand In Sleep Aid Liquid And Solid Sectors

Sales across the total category of consumer health sleeping aid products grew nearly 4 percent to $722m in the 52-weeks ending May 14, according to market research firm IRI's data from US grocery, drug and mass market retail chains, military commissaries and select club and discount chains. Below are Chicago-based IRI's sales data for subcategories and for top sellers among OTC drugs and alternative products.

SLEEP AIDS	MANUFACTURER	SALES (MILLIONS)	SALES % CHANGE FROM YEAR AGO
Liquids			
Subcategory total		$141	1.4
ZZZQuil / OTC	Procter & Gamble Co.	$85.9	4.56
Private label / OTC & alternative		$33.8	5.76
Neuro Sleep / alt.	Neurobrands LLC	$11.8	(0.51)
Natrol / alt.	Natrol LLC	$2.69	(46.93)
Dream Water / alt.	Dream Products, LLC	$2.19	(16.98)
Unisom / OTC	Chattem Inc.	$1.72	(32.99)
SnoreStop / alt.	Green Pharmaceuticals Inc.	$0,725	(12.73)
Sleep Solutions / alt.	Sleep Solutions Inc.	$0,427	30.73
Tablets/Gels/Pills			
Subcategory total		$580.9	4.5
Private label / OTC & alternative		$222	3.01
ZZZQuil	Procter & Gamble	$36.4	(5.08)
Unisom gels	Chattem Inc.	$31.6	(0.76)
Unisom tabs	Chattem	$16.2	14.85
Unisom minis	Chattem	$3.15	8.90
Unisom melts	Chattem	$3.09	(8.96)
Natrol	Natrol LLC	$54.8	28.67
Nature's Bounty / alt.	Nature's Bounty Co.	$44.1	(2.87)
Nature Made / alt.	Pharmavite LLC	$35.9	5.55
Sundown Naturals / alt.	Rexall Sundown Inc.	$21.2	12.71
Vitafusion (gummy) / alt.	Church & Dwight Co. Inc.	$12.9	46.09

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
FDA biotechnology activities related to plant-derived food and animals and report from the National Antibiotic Resistance Monitoring System Review Subcommittee	Science Board	June 26
Pfizer's *Mylotarg* (gemtuzumab ozogamicin) in combination therapy with daunorubicin and cytarabine for the treatment of adults with previously untreated, de novo acute myeloid leukemia	Oncologic Drugs	July 11
Novartis' tisagenlecleucel-T suspension for treatment of pediatric and young adults ages 3-25 years with relapsed/refractory B-cell acute lymphoblastic leukemia	Oncologic Drugs	July 12
Amgen's ABP 215, a proposed biosimilar to Genentech/Roche's *Avastin* (bevacizumab)	Oncologic Drugs	July 13 (morning)
Mylan's MYL-1401O, a proposed biosimilar to Genentech's *Herceptin* (trastuzumab)	Oncologic Drugs	July 13 (afternoon)
Safety and efficacy of Dynavax's hepatitis B vaccine	Vaccines and Related Biological Products	July 28
Janssen Biotech's *Plivensia* (sirukumab) for adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more disease-modifying anti-rheumatic drugs	Arthritis	Aug. 2

Pink Sheet

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