Biosimilar Barricade Breached: Amgen Manufacturing Patents Ruled Not Infringed

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Apotex Inc. has eliminated a legal roadblock to launching its biosimilars to Amgen Inc’s Neulasta (pegfilgrastim) and Neupogen (filgrastim) but still has to convince FDA to clear its applications.

Judge James Cohn of the US District Court for the Southern District of Florida ruled that Apotex’s biosimilar candidates do not infringe Amgen’s manufacturing process patent, No. 8,952,138, which covers a process of protein refolding. The patent was issued by the Patent and Trademark Office in February 2015 and expires in 2031.

The ruling is a reversal of sorts for Amgen, which had won a victory in July when the court ruled in support of the patent’s validity on several grounds. The same day of that decision, Apotex filed a motion asking the court to find that its protein refolding process does not infringe the ‘138 patent.

The Sept. 6 decision of noninfringement appears to be the first ruling on whether a biosimilar sponsor’s manufacturing process infringes the originator’s patent. While the finding is specific to the manufacturing issue in the case it shows that biosimilar sponsors can get around manufacturing process patents, which can be one of the last barricades to biosimilar competition once a composition of matter patent expires.

Irena Royzman, a partner at Patterson Belknap Webb & Tyler, said it is hard to say anything general about the ruling other than that undoubtedly biosimilar makers may make efforts to design around manufacturing process patents.

“Manufacturing patents can make a difference between being able to bring a product to market and not,” she said. “It depends on the patent.”

PROTEIN CONCENTRATION IS NOT THE SAME

Judge Cohn concluded that Apotex’s manufacturing process differs from that covered by Amgen’s patent, citing the protein concentration in Apotex’s refold mixture.

“Amgen has not met its burden to prove that Apotex’s process for manufacturing its filgrastim and pegfilgrastim products meets each and every claim limitation of the ‘138 patent. Specifically, Amgen has not proven by a preponderance of the evidence that Apotex’s process literally meets the protein concentration claim limitation or equivalently meets the redox buffer strength claim limitation.”

The judge said Amgen also did not show infringement under the doctrine of equivalents, whereby the elements in the process are found to be identical or equivalent to those claimed in the patent.

The ruling says batch records show that in the 91 times that Apotex has run its manufacturing process, the average protein concentration is not the same.

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The balance of power behind the prescribing decision is changing: payers are ever more in charge. That means that insight into how payers make decisions – how they evaluate drugs, one against another – will be crucial to any successful drug launch.

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UK Accelerated Access Proposals Due Out Soon
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UK proposals to promote innovation and speed access to promising new drugs could among other things prompt new payment models. The final report on the government’s Accelerated Access Review should be out by the end of the month.

EpiPen Medicaid Rebates Could Increase As Mylan, CMS Dispute Heats Up
Mylan, agency take opposing views on whether the company has been overcharging Medicaid for EpiPen, which is currently classified as a generic for the purposes of program rebates.

Indonesian Patent Changes Favor Generics As Country Builds Up Domestic Industry
http://bit.ly/2c1DOd3
Changes to the Patent Law, alongside measures to increase domestic raw material manufacturing and introduce a universal healthcare scheme, are expected to give a substantial boost to the generics sector in Indonesia.

FDA Urges Firms To Control Metal Impurities From Equipment And Containers
http://bit.ly/2cgZU5i
Drug makers working to comply with new ICH Q3D metal impurity standards should pay special attention to the possibility of metals leaching from manufacturing equipment and container closures, an FDA official says at agency workshop.

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content in Apotex's inclusion bodies has been 36%, with the balance of Apotex's inclusion bodies – on average, 64% by weight – being water. In addition, it says the highest protein concentration in the refold mixture has been 0.56 g/L, which is well below the patent claim of “at or above 1g/L.”

Amgen filed suit against Apotex in August 2015 alleging that Apotex's biologics license application for its Neulasta biosimilar would infringe the '138 patent and the composition patent No. 5,824,784, which expired in October 2015.

In its July ruling, the court found the '138 patent was not invalid for anticipation, lack of written description, indefiniteness, and obviousness but made no judgment on a claim of invalidity based on lack of enablement. In his Sept. 6 decision, Judge Cohn declined to issue an opinion as to whether the patent is invalid for lack of enablement, saying this was not plainly evident based on the evidence presented at the bench trial.

In his current Apotex ruling, Judge Cohn also denied Apotex an award of attorney's fees. He noted that the fees to the prevailing party may be awarded only in exceptional cases and this was not such a case.

“Amgen's actions in asserting its patent rights were reasonable,” the judge stated. “Amgen advanced a cogent argument for a finding of infringement, and it should not be penalized simply because the court found Apotex's evidence and arguments more convincing. Furthermore, Amgen litigated the case in a reasonable and professional manner.”

Amgen declined to comment on the litigation and whether or not it will appeal.

**UNKNOWN HURDLES AT FDA**

While Apotex has made headway with the courts, its biosimilar applications have been tied up at FDA. It submitted its pegfilgrastim BLA in October 2014 and its filgrastim application in December 2014.

The company has not disclosed any FDA action on the proposed biosimilars but FDA’s latest Biosimilar User Fee Act Performance Report suggests the agency issued a “complete response letter” for its pegfilgrastim within the 10-month review period and it is likely Apotex received a letter for filgrastim as well since the user fee action date has long passed.

Any biosimilar launch will be delayed another six months as the US Court of Appeals for the Federal Circuit recently ruled that the company must provide Amgen 180-day's notice of commercial marketing after FDA approval.

Given Apotex's silence on the applications it is unknown what issues are delaying licensure and whether they can be readily addressed, but the product appears to be challenging one for other biosimilar sponsors as well.

FDA approved Sandoz Inc's filgrastim application last year and its product, Zarxio (filgrastim-sndz), is the only biosimilar to have launched in the US. Its pegfilgrastim application has also hit a roadblock as the company announced in July that it had received a complete response letter from FDA. Coherus BioSciences Inc. also submitted an application for a proposed pegfilgrastim biosimilar last month.

**BATTLES OVER CELL CULTURE MEDIUM PATENTS**

In another case, Amgen filed suit against Sandoz in May in the Northern District of California alleging infringement of two other Neulasta patents, No. 8,940,878 claiming a method of purifying proteins used in the manufacture of a biologic product, and No. 5,824,784, which claims a biological product and the use of and manufacturing of a biological product.

Manufacturing process patents are routinely being asserted in biosimilar litigation. In another case, Janssen Biotech Inc. is claiming Celltrion Inc. and partner Pfizer Inc's Remicade (infliximab) biosimilar infringes a patent covering a particular cell media culture. The patent, No. 7,598,083, expires in February 2027. Janssen won a favorable ruling in a Markman hearing as to the meaning of “cell culture media” and a trial on that patent is scheduled to begin on Feb. 13.

Meanwhile, Pfizer is expected to launch its biosimilar to Remicade, Inflectra (infliximab-dyyb), next month. Pfizer agreed not to launch before Oct. 3, 180 days after FDA approved the product.

Amgen is also tussling with Hospira Inc. (now Pfizer) over access to documents that it says would enable it to determine if the cell medium culture used in manufacturing Hospira's biosimilar for Epogen (epoietin alfa) is infringing its cell culture medium patents. Delaware District Court Judge Richard Andrews denied Amgen's motion to compel Hospira to produce the information and limited discovery to the two patents at issue in Amgen's suit against the company.

Amgen appealed the decision to the Federal Circuit and Hospira filed a motion to dismiss the appeal on the grounds that the district court has not issued a final judgment on the case. In an Aug. 12 order, the Federal Circuit denied Hospira's motion and asked the parties to address in their briefs whether the court has jurisdiction in the matter.

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**Medicare Part B Demo Partially Shielded From Congress By CBO Scoring**

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The Congressional Budget Office is thwarting efforts by Republicans in Congress to block the progress of the controversial Medicare proposal to test new reimbursement approaches for Part B drugs.

The leadership of the House Budget Committee expressed frustration with CBO at a Sept. 7 hearing called to challenge the office’s projections that the Center for Medicare and Medicaid Innovation (CMMI), the organization responsible for developing the Part B experiment, would produce $34bn in savings by 2026 through its work.

Although no one expects that legislation interfering with the activities of CMMI will be enacted this session, a CBO score attaching significant savings to the organization could undercut future efforts by Congress to repeal the organization or scale back its experiments.

Many in Congress have become increasingly alarmed at the broad authority given to CMMI by the Affordable Care Act. The office (or CMS) has the power to waive certain laws in order to conduct experiments in new payment models, can make participation in the models mandatory for providers and patients, and can expand the experiments if they are considered to be successful at saving money while preserving quality or enhancing quality and keeping costs level.

**NEED TO FIND SAVINGS ELSEWHERE**

CBO’s $34bn savings projection is based in part on that broad authority, Deputy Director Mark Hadley explained in written testimony prepared for the hearing. It reflects CBO’s “judgments of how effectively the center will identify, refine, and expand approaches that reduce spending,” he said.

However, the projection is not based on current or planned demonstration projects, such as the Part B drug demonstration. “CBO is monitoring the center’s implementation of demonstrations and will update its assessments as more information becomes available,” Hadley noted. CMS released a proposed rule on the Part B experiment in March. A final rule is pending.

CBO’s score and Hadley’s comments suggest that Congress would need to find a significant amount of savings elsewhere to replace the projected savings that would be lost if legislation repeals CMMI altogether or specifically blocks the Part B demo. Lawmakers are bound by “pay as you go” rules requiring that a new proposal impacting the federal budget must either be “budget neutral” or offset with savings derived from existing funds.

Committee Chairman Tom Price, D-GA, said in his prepared opening statement that CBO’s analysis “tells us that any altering of CMMI’s demonstration activities would result in a substantial loss of savings. CBO appears to come to this conclusion by assuming that CMMI’s abilities to produce savings supersede those of Congress.”

“What concerns this committee and others is the certainty with which CBO’s analysis seems to project substantial savings by CMMI in the future,” Price added. “Those yet unrealized supposed savings make it a challenge for policymakers to propose changes to the program; which in turn, makes it challenging for policymakers to exercise our oversight authority.”

And “because we believe seniors on Medicare ought to have access to the life-improving and life-saving treatments their doctors recommend, it is important that we ensure Congress is able to exercise its oversight authority,” Price maintained.

**PART B DEMO EXPECTED TO GENERATE BIG SAVINGS**

Hadley told the committee that CBO has not completed a score on the proposed Part B demo. However, he indicated that because the demonstration is currently envisioned as such a large project, it could represent a substantial amount of savings that CMMI would look to generate elsewhere if the project is blocked.

“Because [the Part B drug demo] is so large, we also have to look very carefully at the substitution that would occur. That is, in the context of a CMMI project, if that project were to be blocked by Congress or the courts or somebody else, you would expect that CMMI would then pursue other projects and there would be savings from those other projects and that should be credited to the bill,” he pointed out.

The biopharmaceutical industry, physicians and patients have
Reimbursement

The Clinton Drug Price Board, 23 Years Later

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Presidential Candidate Hillary Clinton is getting very specific with her drug pricing proposals, including a new plan unveiled just before Labor Day weekend in response to the headlines about Mylan Pharmaceuticals Inc’s EpiPen.

The centerpiece of the new plan is a new federal oversight board, consisting of “representatives of Federal agencies charged with ensuring health and safety, as well as fair competition, to create a dedicated group charged with protecting consumers from outlier price increases.” The board would be charged with identifying products with “an unjustified, outlier price increase” and take steps to encourage competition and impose penalties on the sponsor deemed guilty of outrageous price increases.

The proposal brings back memories of an earlier Clinton plan to establish a new oversight board for drug prices: in the then First Lady’s 1993-94 health reform effort, one feature would have been a “breakthrough” drug pricing board.

This may be a case where the differences are more important than the similarities. Two decades ago, the focus of the board would have been investigating “unreasonable” prices for a “significant advance over existing therapy.” The current Clinton plan, in contrast, focuses specifically on older, off-patent brands. (The briefing document issued by the Clinton Campaign specifically cites Mylan’s EpiPen and Turing Pharmaceuticals AG’s Daraprim pricing controversies as prompting development of the plan.)

On the surface, the Daraprim and EpiPen controversies seem like almost polar opposite situations. Daraprim was a decades-old product acquired and immediately re-priced at many multiples of the prior price, while EpiPen is a rescue-product for use in emergency situations where the manufacturer, Mylan (which acquired the product from Merck KGAA in 2007), took large, steady price increases over almost a decade.

However, they share one important common characteristic: both are old brands, long off-patent, with no substitutable generic competition. That makes the products outliers from the core of the innovator biopharma sector.

It also means that there are potential levers for an administrative or legislative response that would not be available in the context of still-patented new therapies.

While Clinton’s broader drug pricing plan includes proposals to address new, innovator therapies, the new plan appears to rely on the absence of enforceable patents as a key element of the response.

The timing of the announcement on Sep. 2 ensured media attention on a slow news day – though it also meant a limited audience heading into Labor Day weekend, suggesting an attempt to test a potential campaign theme rather than a full commitment to pricing themes heading into Election Day.

While the biopharma industry is unlikely to support any form of price oversight board, if the new Clinton proposal were to be enacted its focus on older brands makes it far from a worst case scenario.

It is a heck of a lot better than a “Breakthrough” drug price board.

From the editors of the RPM Report. Published on September 6, 2016.
Big Pharma’s Unlikely Price Pledge Leader

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It really is starting to feel like 1993 all over again. First, there is Hillary Clinton proposing a pricing oversight board in response to outrage over perceived excessive price increases. And now you have a Big Pharma company pledging voluntary restraint in annual price increases in an effort to stave off federal regulation.

In the early 1990s, the price pledges were initiated by Merck & Co. Inc., and eventually embraced by almost all of the major pharmaceutical companies of that era. In 2016, the pledge has been made by Allergan PLC – whose CEO Brent Saunders outlined “our social contract with patients” in a Sept. 6 blog post.

As with the Clinton price oversight board, it is interesting to compare the details of the 2016 version of the policy to its predecessor two decades ago. In the case of the pricing board, the most important point is the difference: Clinton is now focusing on addressing price increases for off-patent brands. Two decades ago, the proposed board would have focused on launch prices for breakthrough therapies.

1.7% vs 9.9%

The differences between the modern version of the pricing pledge from its 1990s predecessor are also instructive.

First, there are some telling differences in the policy itself. Merck originally pledged (in 1990) to maintain its average price increase for its entire product line in the range of the overall consumer price index. Over time, that pledge was refined to what became the industry standard during the Clinton health reform debate: Merck would limit any individual product price increase to no more than 1% above the CPI.

Allergan’s pledge is similar – but definitely not the same – as that promise. Instead, Allergan has pledged that it will not raise any product price more than one time during the year, and that the price increase will always be a “single-digit percentage.” Moreover, “our expectation is that the overall cost of our drugs, net of rebates and discounts, will not increase by more than low-to-mid single digits percentages per year, slightly above the current annual rate of inflation.”

On the per-product level, the Allergan policy allows for considerably larger price increases than the final version of the Merck pledge would if applied in the current era. In 2015, the CPI was just 0.7%, meaning that the Merck formula would permit a maximum price increase of just 1.7% per product – well below the 9.9% Allergan is allowing itself.

Moreover, the inflation climates were very different. In 1990, double digit inflation wasn’t a ridiculous concept (the CPI grew by 10% or more every year from 1979-1981), and in fact the CPI in 1990 was over 6% – far higher than in the past decade. When Merck said it would limit price increases to no more than 1% above inflation, it was intended to be a very narrow difference; now it would potentially allow for price increases at twice the rate of inflation.

Still, the overall intent of the pledge sounds very similar to Merck’s original commitment in 1990 – and could certainly end up being revised to be more explicit about limiting individual product price increases if it gains traction in the context of discussion with legislators and the new Administration.

PEDIGREE OF THE PLEDGE-MAKER

The more interesting difference is in the image and pedigree of the pledge-maker.

In 1990, Merck was annually ranked as one of America’s most-admired companies, and its CEO Roy Vagelos liked to appear in his white lab coat emphasizing his background in research. Merck was wildly popular on Wall Street based on its track record of growth – but it prided itself on that broader public image as a company that put patients before profits.

Saunders, like Vagelos, is a charismatic presence and very popular on Wall Street. But his own background couldn’t be more different: a JD and MBA with a background in compliance, consulting, business development and marketing – not a PhD with a background in R&D.

And Allergan in 2016 couldn’t be more different in its image than Merck in 1990. The Allergan name, of course, is most closely associated with Botox – a product with many important therapeutic uses but most widely known as an anti-wrinkling agent. For most of the public, the pricing pledge is likely to be interpreted as applying to a cash-only product used for cosmetic reasons.

Of course, that’s not an accurate description of the contemporary Allergan product line. But the confusion is understandable given the unusual corporate history involved.

A HISTORY OF TAX INVERSIONS

The contemporary Allergan is the result of two mergers, first of Forest Labs and Actavis, and then Actavis and Allergan. As a result, Saunders has gone from CEO of New York City based Forest Labs to running a company whose heritage is in California (Allergan) but whose headquarters are in Dublin.

What those transactions had in common was the desire to structure the merger to allow for a tax inversion.

Allergan was most recently involved in a potential merger to allow Pfizer to reincorporate as a non-US firm, a transaction that was called off after the US Treasury took steps to assure that the intended tax treatment would not apply.

None of that undermines the potential importance of voluntary pricing pledges in 2016. The strategy definitely helped the industry weather the political storm two decades ago. But it will be interesting to see whether Allergan is able to play the role as the leader in corporate responsibility as comfortably as Merck did a generation ago.

From the editors of the RPM Report. Published on September 7, 2016.
Eisai’s Halaven Faces Another Reimbursement Roadblock In Germany

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The German Institute for Quality and Efficiency in Health Care (IQWiG) has returned a verdict of “no additional benefit” regarding the use of Eisai Co. Ltd.’s cancer drug Halaven (eribulin) in patients with unresectable advanced or metastatic liposarcoma.

Eisai has expressed bewilderment over IQWiG’s report, which the company claims has ignored “pivotal Phase III data which demonstrated clearly that eribulin is the first and only single agent therapy to show a statistically significant overall survival advantage in advanced liposarcoma.”

IQWiG’s verdict for Halaven is a similar to the outcome for the drug when it was assessed by the appraisal body for use in breast cancer. In that case, Germany’s Federal Joint Committee (the G-BA), which makes the final decisions on whether drugs should be reimbursed by state health insurers, eventually endorsed the drug against IQWiG’s recommendations.

The G-BA will make the final decision for Halaven for its liposarcoma indication, due by the end of December this year.

Patrik Höller, director oncology business group at Eisai GmbH, said: “Eisai cannot understand the suggestion of the IQWiG that no additional benefit has been proven for eribulin, despite compelling Phase III data which show an overall survival benefit. We are hopeful that, notwithstanding the report by IQWiG, the G-BA will take a more informed view.”

IQWiG’s negative verdict appears to focus on the fact Eisai only presented studies that compared Halaven directly to chemotherapy agent dacarbazine.

IQWiG’s negative verdict appears to focus on the fact Eisai only presented studies that compared Halaven directly to chemotherapy agent dacarbazine. Also, in Eisai’s studies the use/dosing of dacarbazine was not compliant with its label. Furthermore, the indirect comparisons presented for Halaven versus Johnson and Johnson’s Yondelis (trabectedin) were not accepted due to differences in study populations (IQWiG and the G-BA’s usual reason for rejecting indirect comparisons).

According to analysts from Datamonitor Healthcare, the G-BA’s identified comparator therapy was “patient specific therapy decided by the physician” – meaning Eisai did not present suitable evidence. It is possible the G-BA may relax its stance on the comparison versus dacarbazine comparison when it determines a final verdict for the product in December.

Halaven’s approval for liposarcoma in Europe is based on Study 309, which showed that patients treated with Eisai’s drug compared to those treated with dacarbazine, an established and internationally accepted treatment option, benefitted from a median 7.2 month increase in overall survival for the pre-specified subgroup of patients with unresectable advanced or metastatic liposarcoma (15.6 months versus 8.4 months, p=0.0006).

Liposarcoma represents the most common subtype of soft tissue sarcoma. Furthermore, according to European Society for Medical Oncology guidance, sarcoma represent about 1% of all cancers diagnosed in Europe. Germany is a valuable market for Eisai to access for Halaven in this latest indication as approximately 3,000 people in Germany are diagnosed with soft tissue sarcomas each year.

Halaven was approved in Europe in May 2016 for use in patients with unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease. It is also licensed in Europe for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease.
China Clarifies Position on Forged Trial Data As 30 Applications Are Rejected

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The China Food and Drug Administration has rejected 30 new drug applications following last year’s crackdown on companies that submit suspect data. In addition, the agency has issued for consultation a draft guidance that seeks to clarify what constitutes data forgery and what the legal consequences are for wrongdoers.

The 30 applications were turned down, in most instances, because of findings of “false clinical data,” said Katherine Wang, of law firm Ropes & Gray.

They were rejected as part of the inspections the CFDA has been conducting in relation to study sponsors who, in July 2015, were ordered to self-audit their clinical trial data and their compliance with good clinical practices (GCP).

Sponsors of a total of 1,622 drugs pending approval at the agency had been told to conduct the self-audits in a CFDA circular that had taken industry by surprise.

Around 80% of the pending new drug applications were subsequently withdrawn voluntarily by applicants, with domestic drug makers accounting for around 90% of the total.

The CFDA began inspecting the remaining products in early 2016 and it reported in an Apr. 29 notice that it had rejected six new drug applications based on various clinical data violations. According to Ropes & Gray, 30 applications had been rejected following the completion of the first three batches of inspections. Wang said that the agency had initiated five rounds of onsite inspections of selected clinical trials, including some Phase I to III trials and some bioequivalence studies.

GUIDANCE AIDS TO REMOVE AMBIGUITY

Regarding the agency’s new draft guidance, issued Aug. 24, the agency is seeking to clarify what constitutes data forgery and the legal consequences of noncompliance in clinical trials for different stakeholders.

Wang explained that even though China’s recent drug regulatory reform had emphasized that clinical trial data must be “authentic and reliable,” the legal consequences for breaching data integrity requirements in clinical trials had remained ambiguous.

The draft guideline seeks to clarify, among other things, that sponsors will be considered to have committed data forgery if they hide certain trial data or do not present the complete data set in their marketing applications.

It also makes it clear that the sponsor ultimately bears all the legal liabilities for the submitted clinical data and drug application dossier, said Wang, a partner at the Shanghai office of Ropes & Gray. Meanwhile, study sites and CROs will bear liability for data integrity issues for which they are directly responsible.

Trial data forgers will be banned from refiling an application for the same product with the CFDA for the following three years, Wang said. “In particular, if data forgery is found to have occurred after November 11, 2015, the CFDA will directly reject the current application under review, and the applicant will be banned from filing any applications for any drug products for one year.”

The draft guideline also deals with blacklisting wrongdoers. “Blacklisting will apply not only to the sponsors, sites and CROs involved in data forgery, but also to the responsible individuals within these entities,” the Ropes & Gray lawyer noted.

Wang said that companies should “arrange necessary audits of ongoing clinical trials, evaluate the level of GCP compliance, and develop corrective action plans accordingly.”

“Applicants can be exempted from penalties if they voluntarily report all identified issues through self-inspection and withdraw the questionable applications,” she explained, adding that there would be “leniency in penalties if applicants fully cooperate with the investigation and timely explain and correct the identified noncompliance.”

On the other hand, she warned, applicants who decline, deter, or avoid inspections can face higher penalties.

As for the wrongdoings disclosed by the CFDA in its Apr. 29 notice, these included severe adverse events left unreported, critical data gone missing, and drugs substituted to pass bioequivalent testing.

The deadline for submitting comments on the draft guideline is Sept. 18.

From the editors of Scrip Regulatory Affairs. Published on September 2, 2016.

Applicants who decline, deter, or avoid inspections can face higher penalties, warns Ropes & Gray Lawyer Katherine Wang.
Korea Green Light For Pfizer’s Novel Breast Cancer Drug

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Pfizer Inc’s novel drug Ibrance (palbociclib) has received regulatory approval from South Korea’s Ministry of Food and Drug Safety for the treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer.

The oral therapy has been cleared for use in the treatment of postmenopausal women with ER+, HER2- advanced breast cancer both in combination with letrozole as an initial endocrine-based therapy for metastatic disease, or in combination with fulvestrant (AstraZeneca PLC’s Faslodex) in women with disease progression following endocrine therapy.

Pfizer Korea said details such as when the drug will be launched and whether it will be covered by the country’s national health insurance have not yet been determined.

Ibrance, a first-in-class small molecule inhibitor of cyclin-dependent kinase 4 and 6 (CDK4/6), was approved in the US in February 2015 for use with letrozole and in February this year in the setting with fulvestrant, for which it had Breakthrough Therapy designation and received a priority review.

An EU approval is still pending and elsewhere in Asia, palbociclib is in Phase II/III development in Japan.

Breast cancer is the second most frequent malignancy type in South Korean women after thyroid cancer. As of 2012, the number of patients with the disease in the country had more than quadrupled to 17,792 from 2000, according to the Korean Breast Cancer Society.

A number of drugs including Roche’s Perjeta (pertuzumab), Herceptin (trastuzumab) and Avastin (bevacizumab), as well as Novartis AG’s Afinitor (everolimus), are already available locally for the treatment of metastatic breast cancer.

BENEFITS, OUTLOOK

CDK4/6 are attractive therapeutic targets because dysregulation of the cell cycle through genetic alterations is a hallmark of several cancers, including breast cancer. When associated with cyclin-D proteins, CDK4/6 are able to phosphorylate and inactivate the retinoblastoma 1 (RB1) tumor suppressor protein, thereby releasing transcription factors needed for DNA replication and subsequent progression through the cell cycle.

Inhibiting the phosphorylation of RB1 arrests cell growth in the G1 phase, preventing further cell growth and proliferation in malignant tissues, according to Informa’s Datamonitor Healthcare, which predicts that Ibrance and late clinical phase candidates abemaciclib (Eli Lilly & Co.) and ribociclib (Novartis AG) will account for 72% of overall market sales in the HR+/HER2- sector in 2022.

The class as whole came under the spotlight at the American Society of Clinical Oncology (ASCO) meeting in June, with Ibrance seen as likely to maintain its leadership position.

Ibrance is seen as having the greatest commercial potential and should reach estimated peak sales of $4.7bn across the US, Japan, and five major EU markets in 2022. Arriving to market much later, abemaciclib and ribociclib will see less substantial growth, achieving revenues of $1.9bn and $1.4bn respectively in 2024, Datamonitor forecasts.

Palbociclib demonstrated an increase in efficacy over the standard-of-care treatment, letrozole, in the Phase I/II PALOMA-1 trial. These strong clinical data, along with the drug’s first-to-market status and its rapid label expansion into relapsed patients in combination with fulvestrant will keep Ibrance’s sales well ahead of abemaciclib and ribociclib, Datamonitor states.

In April, Pfizer announced positive top-line results from the Phase III PALOMA-2 trial with palbociclib. The study met its primary endpoint by demonstrating an improvement in progression-free survival in combination with letrozole compared with letrozole plus placebo in postmenopausal women with estrogen receptor-positive, human epidermal growth factor receptor 2-negative (ER+, HER2-) advanced or metastatic breast cancer who had not received previous systemic treatment for advanced disease.

GROWING MARKET

Datamonitor estimates that the HR+/HER2- breast cancer market will more than triple in value over the 2015–22 period, and sales of drugs totaled $3.4bn across the US, Japan and five major EU markets in 2015. This combined figure is forecast to reach a peak of $10.6bn in 2022 before falling back down to $9.5bn in 2024, increasing at a compound annual growth rate of around 12% over the period.

The growth will largely be due to the rapid uptake of Ibrance and the approval of other pipeline candidates, and Datamonitor predicts that 10 new therapies will launch for the indication over the course of the forecast period. The group of products will feature several different mechanisms of action, indicating a potentially segmented treatment space in the future.

From the editors of PharmAsia News. Published on September 5, 2016.
Heplisav-B Review Still On Track Even After Cancelled Advisory Cmte., Dynavax Says

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FDA cancellation of an advisory committee meeting can often be viewed as an ominous sign of an application’s prospects. However, Dynavax Technologies Corp. suggests a more positive view, saying the agency called off a public review of the adjuvanted hepatitis B vaccine Heplisav-B because the meeting was not necessary for a timely regulatory action.

In a notice posted on FDA’s website on Sept. 2, the agency said the Nov. 16 meeting of the Vaccines and Related Biological Products Advisory Committee to discuss and make recommendations on Heplisav’s safety and efficacy “has been cancelled to allow time for the FDA to review and resolve several outstanding issues.”

“The agency intends to continue evaluating and will schedule an advisory committee meeting in the future, as needed,” the notice states.

“Remaining questions will be addressed between Dynavax and the review team via the normal process,” the company said.

The timing of the cancellation announcement was odd because FDA only just officially announced the meeting date and topic in an Aug. 30 Federal Register notice. Dynavax, however, had informed the investment community of the meeting date in an Aug. 5 press release.

FDA said it could not discuss the progress of its review efforts for the BLA. “Federal disclosure regulations prohibit the FDA from commenting on the product application beyond the information posted about the cancellation of the advisory committee meeting,” the agency said.

Dynavax did not immediately respond to press questions about the meeting cancellation. However, the news instantly increased questions about the firm’s ability to secure FDA licensure by the application’s Dec. 15 user fee goal date – a timeline that already has seen one three-month extension.

The company’s stock got hammered on news of the meeting cancellation, losing almost 32% of its value and closing at $10.91 on Sept. 2.

DYNAVAX’S RELATED EXPLANATION
It was not until two days later that the company issued its own statement about the meeting cancellation.

In a Sept. 4 release, the company said that during recent conversations, “the agency communicated decisions to enable compliance” with the Dec. 15 goal date, which remains unchanged. “The agency informed Dynavax that the VRBPAC meeting was cancelled and remaining questions will be addressed between Dynavax and the review team via the normal process.”

“FDA informed Dynavax that it plans to provide information requests related to remaining questions in the upcoming weeks,” the company said. “Dynavax is prepared to address these questions expeditiously in order to enable the FDA to complete its review as soon as possible.”

“Our dialogue with the FDA has been very open and productive, and we look forward to providing the review team with any additional information they may need to complete their review,” CEO Eddie Gray said in the release. “We are committed to bringing Heplisav-B to market as we believe it offers a better level of protection than the currently available hepatitis B vaccines.”

DOGGED BY SAFETY CONCERNS
Heplisav-B combines recombinant hepatitis B surface antigen with 1018, a synthetic cytosine phosphoguanine oligodeoxynucleotide that boosts immune response to the antigen. It is intended to be more potent, given in fewer doses and over a shorter period of time than other hepatitis B vaccines. In clinical trials it was administered in two doses over one month, compared to three doses for GlaxoSmithKline PLC’s Engerix-B vaccine given over six months.

Heplisav and its adjuvant have been the focus of safety concerns, including a case of Wegener’s granulomatosis that led to a temporary FDA clinical hold on the vaccine’s development in 2008. The safety-related hold led development partner Merck & Co. Inc. to return all rights to the vaccine to Dynavax.

The vaccine made its first trip to an FDA advisory committee in November 2012. While panelists voted 13-1 that immunogenicity data supported the product’s efficacy, they voted 8-5, with one abstention, that available data do not support the safety in individuals 18-70 years old, Dynavax’s target population.

Committee members were concerned about the size of Dynavax’s safety database, particularly given the vaccine’s novel adjuvant. The sponsor’s proposal for a 30,000-patient postmarketing cohort safety study was not enough to overcome these concerns.

In February 2013, FDA issued a complete response letter seeking more safety data in the broad population of adults and citing concerns about the adjuvant.

Dynavax considered seeking approval for a more restricted population but opted instead to stick with a broad population.
FDA will not review diabetic subpopulation immunogenicity data in the current review cycle.

**RESUBMISSION BACKED BY NEW TRIAL**

In January, it released positive, top-line data from a new Phase III safety and immunogenicity study (HBV-23) in which more than 8,000 patients were randomized to Heplisav or Engerix.

Heplisav was non-inferior to Engerix on seroprotection rate at week 28, the main immunogenicity measure, and demonstrated a statistically significantly higher rate of seroprotection than Engerix in diabetics, a secondary immunogenicity measure. The peak seroprotection rate for Heplisav also was statistically significantly better in the overall population and all other pre-specified subpopulations analyzed, the company reported.

The company’s March BLA resubmission resulted in a Sept. 15 user fee goal date. However, FDA extended the review period by three months after Dynavax submitted, at the agency’s request, individual trial data sets that had been provided as integrated data in the BLA resubmission. The agency determined that the addition of these large data sets represented a major amendment to the BLA, the company said.

Bolstered by the results from the HBV-23 trial, Dynavax said it would seek a labeling claim for seroprotection rate superiority compared to Engerix, particularly with regard to the subpopulation of patients with type 2 diabetes. However, it now appears that the diabetes data will not be reflected in initial labeling if the vaccine is licensed.

FDA “confirmed to Dynavax that it will review the overall immunogenicity data from HBV-23, the company’s most recent pivotal Phase III trial, to support the proposed indication for adults 18 years of age and over,” the company said.

“However, the agency has decided it will not review immunogenicity data related to subpopulations including results in individuals with diabetes because these data were not a direct response to the FDA’s Feb. 22, 2013 complete response letter and therefore fell outside of the review time allocated to a Class 2 resubmission,” Dynavax said. “It was suggested the data should be submitted as a supplemental BLA following approval.”

*Published on September 6, 2016.*

**FDA’s ANDA Approvals**

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**Tentative Approvals**

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UK MHRA Adapts Inspections Program To Account For Increase In Pharmacovigilance Outsourcing

VIBHA SHARMA  vibha.sharma@informa.com

The UK Medicines and Healthcare products Regulatory Agency has introduced changes to its current approach to good pharmacovigilance practice (GPvP) inspections so that problems identified at third-party pharmacovigilance service providers are properly communicated to all affected marketing authorization holders using their services.

The MHRA explained that under the earlier approach it had observed that pharmacovigilance service providers performed only partial remediation to address issues identified at specific MAH inspections and that the agency’s inspectors did not routinely request broad impact assessments and remediation across the service provider system/organization as part of the corrective and preventative action (CAPA) plan for MAH inspections.

This issue has now been addressed so that “where significant issues are identified relating to the activities of [third party] service providers during an MAH inspection, the MHRA can request broader impact assessments from the service provider and relevant CAPA, as well as perform standalone inspections of the service provider where appropriate,” an agency spokesperson told the Pink Sheet.

Where appropriate, the spokesperson explained, MAHs are encouraged to share inspection reports with relevant service providers to whom they have subcontracted pharmacovigilance activities. “As part of the inspection report, service providers are reminded that deficiencies that are more broadly applicable to MAHs that were not subject to the inspection concerned may need to be shared with those affected, such that appropriate CAPA can be derived;” the spokesperson added.

The changes were introduced in mid-August after the agency shelved its proposal to conduct dedicated standalone inspections of pharmacovigilance service providers in return for a fee.

The activities of such service providers are scrutinized as part of the agency’s inspection of the concerned MAH, who pays the fee. The MHRA had hoped that conducting standalone inspections of the service providers would cut down the inspection costs incurred by MAHs (who hire such third-party service providers) and would also save agency resources.

Following a feasibility pilot, however, the MHRA concluded that “there are a number of challenges” in conducting standalone inspections and decided not undertake them on a routine basis, said Richard Andrews, unit manager of MHRA’s GMP/GPVp Inspectorate, speaking at the MHRA’s GPvP Symposium in London on Sept. 2.

The MHRA, however, acknowledges that MAHs are increasingly outsourcing some or all of their pharmacovigilance activities to contract service providers and that these activities “need to be subject to some sort of supervision by the MHRA,” he added.

CHALLENGES OF A STANDALONE INSPECTIONS PROGRAM

During the feasibility pilot, the MHRA found that while contract service providers often implement core processes that are used for all of their clients, they also often establish some client-specific processes.

Specifically, the MHRA found that “a review of client-specific activities undertaken by a service provider in the context of a MAH inspection” is almost always necessary. This means that a single inspection of a service provider’s general system and procedures may be insufficient to demonstrate GPvP compliance across a number of MAHs.

The feasibility pilot also showed that the interfaces between service providers and MAHs, and the exchange of information, are crucial in establishing a compliant pharmacovigilance system. “It is challenging to inspect these specific interfaces in the context of a standalone service provider inspection without involvement of the MAH(s), again negating the benefits and becoming practically difficult. These aspects may need to be assessed in the context of a MAH inspection,” the agency said in a blog post.

The pilot also showed that a routine standalone inspections program would not offer sufficient benefit in terms of a tangible reduction in inspection resources required to assess the activities conducted by service providers, versus the current model where the activities are assessed in the context of individual MAH inspections.

From the editors of Scrip Regulatory Affairs. Published on September 5, 2016.
All Roads For OTC Policy Improvements Lead To User Fees, FDA Suggests

MALCOLM SPICER  malcolm.spicer@informa.com

A ll roads lead to user fees as far as improving FDA’s process for adding ingredients or indications to OTC drug monographs, Center for Drug Evaluation and Research officials’ comments to industry stakeholders suggest.

“There’s simply not enough appropriated money to go around for all of the things the agency has to do,” said Donal Parks, director of CDER’s Division of User Fee Management and Budget Formulation, during a Sept. 6 FDA webinar to provide an update on FDA-industry discussions about potential monograph program user fees.

Asked for FDA’s outlook on the monograph process if a user fee program is not established, Parks was blunt: “The industry and the public would suffer.”

“The basic course of action is we keep doing what we’re doing with what we have,” he said. “There’s a lot of work to be done but not a lot of resources for it.”

Some industry stakeholders have been wary of endorsing the fees before there are more details on how the monograph process would be improved. Nonetheless, the OTC industry appears to take it to heart that a new source of funding is necessary, said Karen Mahoney, deputy director of CDER’s Division of Nonprescription Drug Products. Drug firms’ opportunities to introduce new nonprescription products, other than through Rx-to-OTC switches, are inhibited by limited FDA funding for the monograph process.

“FDA and the industry have known for a long time that the OTC monograph review is significantly under-resourced, but over the years the industry has come to realize that this lack of resources isn’t just an FDA issue. It’s also affecting the industry’s ability to do what it needs to do,” Mahoney said during the webinar.

“Impressively interested in innovation. In order or the agency to be able to evaluate innovations, additional resources are needed,” she added.

Mahoney and Park’s comments were consistent with previous agency statements about a lack of funding available for OTC programs since well before floating the idea of a monograph user fee in a Federal Register notice in May. But they offered few details from discussions with industry to establish a fee program that began in July.

FDA’s existing resources include $8.2m for OTC programs in the Center for Drug Evaluation and Research’s fiscal 2016 budget, 18 full-time equivalents in CDER working only on nonprescription drug issues and 12 other FTEs with responsibilities that touch on OTCs.

Those levels of resources appear even more limited when considering FDA’s overall mission, with priorities often determined by considerations other than innovation. “Currently FDA must focus its resources on public health emergencies and external mandates,” Mahoney said.

She suggested policymakers would see a “compelling case” for user fees to improve the monograph process, perceiving that the availability of more consumer health care products is a public health benefit.

The House Energy & Commerce Committee Democratic chief of staff noted recently that the committee considers FDA user fees generally favorably, largely they provide more money for programs without drawing on the federal budget.

Should the OTC drug industry and FDA agree on the framework for a potential fee program, their agreement would be recommended as the basis for legislative enactment. The OTC measure could be tied to the reauthorization of the Prescription Drug User Fee Act in 2017 or the Animal Drug User Fee Act in 2018.

‘CONSUMED BY’ SUNSCREEN, ANTISEPTIC MONOGRAPHS

FDA opened a separate comment document in 2014 for input on how to improve the monograph process. But there too, the agency emphasized that a dearth of monograph actions over the past 10 years made outside of targeted legislation or a consent decree following litigation reflects a lack of resources for the agency as much it shows problems with the process.

Legislation set deadlines for FDA to review potentially adding ingredients to the sunscreen monograph. And a 2013 consent decree eventually led to the Sept. 2 final rule establishing 19 active ingredients as not generally recognized as safe and effective for use in consumer antiseptic wash products.

But Mahoney pointed out that said “we have dozens if not scores of” other monograph changes or additions to consider. “Being consumed by just two or three makes it very difficult for us to attend to our overall mission,” she said.

And the monograph mission is made difficult by the program’s regulatory framework that requires formal rulemaking for any change, a point CDER Director Janet Woodcock has made.

“That has to do with the extreme difficulty with the current rulemaking process. It has been very difficult to go through the rulemaking process to add new ingredients,” Mahoney agreed.

In addition to a potential OTC monograph user fee, personal care and cosmetic product firms could be subject to a separate user fee under Senate legislation that also would require facilities registration, product and ingredient statements and submitting serious adverse event reports to FDA.

From the editors of the Tan Sheet. Published on September 7, 2016.
B. Cepacia Hits ICUs Again, Raises Manufacturing Controls Questions

Bowman Cox bowman.cox@informa.com

The mystery began in June. In one intensive care unit after another, one hospital after another, one state after another, patients on ventilators were contracting serious infections from an opportunistic pathogen best known for rotting onions.

By Aug. 10, the outbreak had expanded to 60 confirmed cases in eight states.

Investigations by local, state and federal health authorities to determine why it was happening and how to stop it led them into one of the US market’s murkier global pharmaceutical supply chains.

It’s a case that serves as a potent reminder for manufacturers to guard their supply chains against contamination threats, even for pharmaceutical products that pose little risk in most circumstances, and even from organisms that are harmless for most people.

HOW PATIENTS WERE GETTING INFECTED

Because the opiates that patients in ICUs receive for pain management can cause constipation, their health care teams give them laxatives. Because the patients can’t swallow tablets or capsules while they are on ventilators, the laxatives come to them as liquids through nasogastric tubes.

Physicians have a choice of laxatives, but the infected patients all received the same type, docusate sodium.

FDA, which periodically has been posting updates about the outbreak, said July 8 that it had tested multiple liquid docusate products that were epidemiologically linked to reported cases, and found that they all contained one or two outbreak strains of the onion-rotting Burkholderia cepacia complex, often called Bcc or simply B. cepacia.

The next challenge would be to root out the source of the contamination, and that’s where things got murky.

OTC SUPPLY CHAIN MEMORY HOLE

There are no applications on file with FDA for approval to manufacture docusate sodium, no data on file regarding who is manufacturing it or where they are obtaining their active ingredient or how they’re making sure it’s not contaminated.

The reason: years ago, FDA proposed to consider docusate sodium generally recognized as safe and effective for over-the-counter use, at least for certain dosage ranges. Anyone can manufacture it for the US market using API from any supplier they choose without prior approval from FDA.

OTC drug manufacturers and their API suppliers are subject to inspection for GMP compliance, but they’re often not FDA’s first priority to inspect. After all, by definition their products are considered low risk. And in any case, the agency may not necessarily know the firms exist, or that they sell product in the US, or to wholesalers or distributors who in turn sell product to US retailers.

A RECALCITRANT FOE

B. cepacia preys on the ill, and can be very difficult to identify and remove from pharmaceutical manufacturing facilities and products.

But there are preventive measures FDA looks for manufacturers to take when it reviews their applications.

In October 2013, John Metcalfe, an FDA microbiologist, gave a Parenteral Drug Association pharmaceutical microbiology conference some insight into how the

FDA’S CONSTIPATED LAXATIVES MONOGRAPH

FDA on Jan. 15, 1985, issued a proposed rule that it called a tentative final monograph on laxative drug products for OTC use, in which the agency tentatively accepted the recommendations of an expert advisory committee.

But after the expert panel submitted its report, the agency learned of animal studies that raised questions about the panel’s recommendations on docusate laxatives.

Rather than delay finalization of the laxatives monograph, the agency removed all discussion of the safety and effectiveness of docusate salts from it.

More than eight years later, after reviewing additional data, FDA on Sept. 2, 1993, proposed to amend the laxatives tentative final monograph with a determination that docusate salts are generally recognized as safe and effective, and not misbranded.

Currently, nearly 13 years after the proposed amendment and more than 31 years after the initial proposal, the laxatives monograph still has not been finalized.

The time that FDA has needed to establish a laxatives monograph is not unusual for the OTC monograph program. The agency is reviewing the program to identify areas of improvement and is discussing with the industry whether establishing user fees would help.
agency expects new drug applicants to show how they would control B. cepacia in aqueous non-sterile drug products.

Although Metcalfe focused his remarks on the application approval process, the measures he described would work just as well for drugs like oral liquid docusate sodium that don’t require FDA approval.

A LONG HISTORY OF PROBLEMS

Metcalfe pointed to a paper that Scott Sutton and Luis Jimenez of the Microbiology Network had published in the American Pharmaceutical Review the year before that analyzed non-sterile drug recalls in 2004-2011. Sutton and Jimenez found that 88% of those 142 recalls were due to poor microbiological quality, and 34% of those (or 30% of the total) were due to B. cepacia.

Metcalfe also called attention to an article in the September-October 2011 issue of the PDA Journal by statistician Lynn Torbeck and FDA microbiologists Diane Raccasi, Dennis Guilfoyle, Rick Friedman and David Hussong calling for the industry to focus on removing the opportunistic pathogen from manufacturing areas and drug products.

The article, part of a series exploring the root causes of drug recalls, came in the wake of a major recall in 2008 of B. cepacia-tainted surgical prep cloths made for decontaminating surgical sites prior to incision. That recall began after B. cepacia grew in the chlorhexidine gluconate disinfectant solution that a supplier provided.

Also that year, another firm recalled B. cepacia-tainted mouthwash that had been distributed to hospitals, medical centers and long-term care facilities, in at least some cases as a component of personal hygiene hospital admission kits. In similar instances in 2005, CDC reported hospital-acquired pneumonia cases in several states from yet another firm’s B. cepacia-contaminated mouthwash.

The maker of the contaminated surgical prep cloths, Sage Products of Cary, Ill., followed an FDA recommendation to add B. cepacia to the list of microorganisms checked in its release testing. FDA argued in a warning letter that the company also should add GMP controls and should reformulate the chlorhexidine gluconate cloths as sterile products.

Sage Products was in the news again last month with a recall of dimethicone-impregnated incontinence care cloths. That product, which like docusate sodium is regulated as an OTC monograph drug, also was contaminated with B. cepacia.

LESSONS LEARNED FROM PAST RECALLS

The PDA article by Torbeck and others presented lessons learned from an analysis of 16 B. cepacia-related drug recalls conducted in 2000-2008:

- B. cepacia infections can be serious for infants, the elderly, people who have compromised immune systems, and those who have chronic lung diseases like cystic fibrosis.
- The median survival rates of people with cystic fibrosis decline markedly with B. cepacia infection, particularly those who receive lung transplants.
- B. cepacia infections can be highly resistant to antimicrobial medications, particularly once they have formed biofilms, making treatment difficult.
- Manufacturers cannot rely on antimicrobial preservatives in drug products to control B. cepacia because it is highly resistant to them, and can even eat them.
- Because B. cepacia thrives in low-nutrient waters but not in high-nutrient culture media, it can easily avoid detection during release testing of non-sterile liquid drug products, only to proliferate later while the products are stored and distributed.
- While it appears that B. cepacia cannot survive for more than a week on a completely dry surface, it can survive for many months in water.
- Of the 16 recalls analyzed, six resulted from various water issues and three from contaminated raw materials, which suggests that manufacturers should focus their attention on those areas.

The paper concluded with this challenge: “Now is the time to remove Bcc from our pharmaceutical manufacturing areas and products.” That was five years ago.

STEPS FDA WANTS MANUFACTURERS TO TAKE

There are certain measures FDA expects manufacturers to take to prevent B. cepacia contamination. The agency looks for such controls when reviewing applications for non-sterile aqueous drug products because cepacia strains “have a well-documented ability to ferment a wide variety of
substrates and are known to proliferate in the presence of many traditional preservative systems,” FDA’s Metcalfe explained.

Metcalfe, who works in the Office of Process and Facilities, a part of FDA’s Office of Pharmaceutical Quality, went on to describe two measures manufacturers of non-sterile aqueous drug products should consider taking to control for the presence of B. cepacia in their product.

1. They should identify potential sources of B. cepacia contamination such as raw materials and the manufacturing environment and develop risk-based sampling procedures and acceptance criteria.

2. They should provide validated test methods and acceptance criteria for demonstrating the drug product is free of B. cepacia, taking care to validate the methods for multiple strains of the species, and to acclimate the B. cepacia cells to the manufacturing environment’s temperature before testing.

Metcalfe explained that while there are no compendial methods for detecting B. cepacia, any validated method capable of detecting the organisms would be adequate. He suggested preconditioning representative strains in water or drug product without preservatives when preparing to demonstrate capability to detect small numbers of the organisms.

Application submissions should describe the preconditioning step used, the total number of inoculated organisms, and details of the test method, including growth medium and incubation conditions, he said.

Metcalfe stressed that there should be enough preconditioning to ensure that the proposed recovery methods will be adequate to recover organisms potentially present in the environment.

Metcalfe told The Pink Sheet Aug. 25 that the advice he gave in 2013 still holds true today, and he added some thoughts regarding active pharmaceutical ingredients.

**SIGNIFICANCE OF AQUEOUS API**

Asked for advice on avoiding B. cepacia-contaminated API, Metcalfe replied that the agency’s main concerns revolve around aqueous process steps in drug product manufacturing.

“Although microbiological control and testing of API is expected, and investigations of product contamination cases include examination of the API, FDA’s main concern with Bcc contamination is focused on the aqueous steps of the non-sterile drug manufacturing process,” he said in an email.

“Consequently, FDA advises manufacturers to pay special attention to those aspects of the manufacturing process that involve water,” he explained. “If the API is aqueous, then special attention should be directed to this step of the process.”

**PHARMATECH RECALL**

A major development in the case of the docusate sodium B. cepacia outbreak came July 15 when a contract manufacturer announced that it was recalling a distributor’s liquid docusate sodium product.

PharmaTech LLC in Davie, Fla., said that after receiving a couple of complaints, it was recalling all non-expired lots of Rugby-branded Diocto Liquid docusate sodium due to risk of B. cepacia contamination.

The company runs three production lines for oral liquid drug products, one of which PharmaTech portrays in a slideshow on its website.

Rugby Laboratories, Livonia, Mich., had been distributing the laxative nationwide to wholesale and retail facilities, including hospitals and pharmacies.

But the PharmaTech recall was by no means the end of the story.

FDA said in a press release the next day that some of the adverse event reports it had received “identify liquid docusate sodium products manufactured by companies other than PharmaTech.”

The agency joined CDC that day in recommending against using any liquid docusate sodium for any medical purpose.

**WHAT OTHER FIRMS WERE INVOLVED?**

Although FDA said other firms’ docusate sodium tested positive for B. cepacia, no firm other than PharmaTech has announced a recall.

Companies don’t always announce the recalls they conduct, though FDA eventually describes them in its monthly enforcement reports.

The agency cannot compel companies to recall drug products. If they are foreign, it can use its import alert authority to block their products from reaching the US market, at least directly. If they are domestic, it cannot seize their drug products without a court order, which takes time and resources and rarely happens.

**A FOCUS ON API SUPPLIERS**

The fact that the same B. cepacia strains are growing in multiple suppliers’ liquid docusate sodium suggests that the contamination may have originated at a company that supplied them all with docusate sodium API, particularly if the API was in liquid form.

CDC acknowledged this possibility in its July 8 update, noting that FDA already was conducting “an ongoing investigation of shared ingredients in the products in question.”

A cursory review of online listings of docusate sodium API providers suggests a wide range of possible sources all over the world. A search at the website for the pharmaceutical supply chain trade show company CPhI produces links to more than 20 docusate sodium API suppliers located in numerous countries. The same search at a website called Tradeindia.com returns 14 suppliers based in India. And there are 70 firms offering docusate sodium API on Alibaba.com, most of them based in China.

**A KNOCK ON LAXACHEM’S DOOR**

One of the firms listed on Tradeindia.com attracted FDA’s interest. By Aug. 11, an agency investigator was knocking on the door of Laxachem Organics Private Ltd., in Ahmednagar, India, a small city about a five-hour drive east of Mumbai.
FDA Rule Marks Consumer Antibac Soaps A Possible Endangered Species

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Industry may have known which way the wind was blowing for triclosan and triclocarban use in OTC consumer antibacterial soaps, but now the pressure is on to demonstrate the safety and efficacy of three remaining active ingredients lest FDA effectively close down the entire category.

The agency released a final rule Sept. 2 establishing 19 active ingredients as not generally recognized as safe and effective for use in consumer antiseptic wash products – those used with water and rinsed off, including hand and body washes – which removes them from the agency’s tentative final monograph.

All 19 ingredients must be phased out over the next year – by Sept. 6, 2017 – and antibacterial soaps relying on them must be reformulated and relabeled without antibacterial claims.

“Our concern all along has been that if FDA continues on this path or mindset, they could effectively ban or limit consumer access” to consumer antibacterial soaps altogether, Sansoni said.

All 19 ingredients must be phased out over the next year – by Sept. 6, 2017 – and antibacterial soaps relying on them must be reformulated and relabeled without antibacterial claims.

According to Sansoni, most consumer antibacterial soaps now feature one of the three ingredients still pending under FDA’s deferred rulemaking specific to their use – namely, benzalkonium chloride, benzethonium chloride and chloroxylenol (PCMX).

Industry now has one year to provide FDA with compelling data backing the substances’ capacity for safe and effective use in the category. Sansoni said industry already has delivered strong study data to the agency and will be submitting more over the next 12 months.

The concern at this point is that the entire category of OTC antibacterial soaps could be targeted for elimination from store shelves, which would deal a significant blow to industry and prevent consumer access to popular products that many believe are...
Critical to public health.

“Our concern all along has been that if FDA continues on this path or mindset against the category of products, they could effectively ban or limit consumer access,” Sansoni noted. Industry stands behind its position that triclosan- and triclocarban-containing soaps are safe and effective, as demonstrated by decades of consumer use, but FDA’s final rule “certainly clarifies the mission,” the exec said. Industry’s focus at this point is squarely on the three active ingredients that remain in question.

**ILLNESS PREVENTION DATA NEEDED**

The task before industry is daunting, and visibility is low into how FDA will receive the data coming its way.

Sansoni noted that when FDA proposed amending its TFM in late 2013 to remove antimicrobial ingredients that lack sufficient evidence of safety and efficacy, it “moved the goalposts” in terms of the type of data needed to demonstrate GRASE.

In particular, the agency indicated that studies linking antimicrobial actives to greater reductions in bacteria counts compared with plain soap and water—which industry has argued demonstrate their superior germ-killing potential—are inadequate to show efficacy.

FDA holds that studies also must demonstrate that antibacterial soaps are more effective at preventing illness and the spread of infection—highly challenging endpoint to verify through clinical trials or other controlled studies.

“It’s a whole new landscape that manufacturers have had to deal with,” Sansoni said. He went on to note the myriad variables that can complicate an assessment of antibacterial products’ ability to defend against illness or infection.

“Consumers use these products in every conceivable location, whether it’s in the home or offices or daycare centers or schools, and they’re interacting with so much in their daily lives, doing literally a million different things—at home, on the way to work, touching things in the subway, going to the office.”

It’s “incredibly difficult” to determine the role that antibacterial soaps play in disease prevention amid this complexity of factors, with so many opportunities for consumers to come into contact with infectious bacteria, he suggested.

Michele urged industry stakeholders to submit progress reports to FDA regarding ongoing studies on the three outstanding antimicrobial ingredients before February 2017, “at which point we’ll reassess timing for a GRASE determination and further rulemaking for these ingredients,” she said.

She noted that FDA’s New Drug Application route is an alternative avenue outside of the OTC monograph system for pursuing use of the non-GRASE ingredients in consumer antibacterial soaps.

**ANTIBAC RUBS DECISION STILL TO COME**

FDA also is reassessing the GRASE status of active ingredients in consumer antiseptic rubs—including hand sanitizers and wipes—under a separate proposed rule issued at the end of June, which gave stakeholders one year to present data supporting continued use.

Antiseptics used in healthcare settings also are under review.

While FDA says finalization of its proposed TFM for OTC antimicrobial drug products has been a priority since its publication almost 40 years ago, the agency’s work on the issue was spurred by a 2013 consent decree that settled a suit brought by the National Resources Defense Council.

The agreement set deadlines for FDA final rules across the product categories into which the TFM has been divided in recent years. FDA committed to issuing the final rule on consumer antibacterial soaps by Sept. 15.

FDA’s final rules on consumer antiseptic rubs and healthcare antiseptics are due by April 15, 2019, and Jan. 15, 2018, respectively.

ACI also has provided and is in the process of submitting more data to FDA to support the safe and effective use of antimicrobial ingredients in those categories, Sansoni said.

NRDC’s mission in filing the suit that got the ball rolling was primarily to get a decision on triclosan, which NGOs have attacked due to research linking the ingredient to endocrine disruption, bacterial resistance and other health concerns.

Personal-care firms have been eliminating the ingredient from products in response to consumer demand, if not regulatory and NGO pressures.

Procter & Gamble Co. announced in 2013 that it would discontinue use of triclosan due to concerns about its efficacy relative to regular soap. According to P&G’s sustainability webpages, the firm has eliminated the ingredient from more than 99% of its products and has “an exit plan for the few remaining uses.”

In 2012, Johnson & Johnson similarly pledged to rid its products of triclosan, despite its “long and extensive history of safe use,” by 2015. J&J indicates on its website that it has followed through on the commitment.

The Colgate-Palmolive Company (Softsoap), Henkel AG (Dial) and Unilever PLC (Lever) are among firms with stakes in the consumer antibacterial soap market.

From the editors of the Tan Sheet. Published on September 2, 2016.

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European Pharmacopoeia On A Mission To Boost Global Presence

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The European Pharmacopoeia Commission has decided to extend the reach of the European Pharmacopoeia (PhEur) by allowing experts from industry, authorities and academia outside Europe to take part in the pharmacopeia’s work.

The move is a response to the “dramatic changes” resulting from increasing globalization over the past 50 years, according to the European Directorate for the Quality of Medicines and Healthcare (EDQM), which publishes the PhEur. It will no doubt also help to boost the influence of the PhEur around the world.

The EDQM’s announcement coincides with the publication this year of the 9th edition of the PhEur, which comes into effect on Jan. 1, 2017. Described by the EDQM as “Europe’s legal and scientific benchmark for pharmacopeial standards,” the PhEur now includes 121 new and 1,403 revised texts.

Suzanne Keitel, director of the EDQM, says that the 9th edition mostly covers chemically defined substances but also has texts on biotherapeutics, vaccines, homeopathics, herbal medicines, and so on, and reflects changes in medical practice and demand, such as the rise in substances used to treat cancer, hypertension and diabetes.

It was produced with input from more than 700 European experts and observers to the European Pharmacopoeia Commission. These experts sit on dozens of expert groups and working parties specializing in topics such as antibiotics, biological and biotechnological products, cell therapy, excipients, and inorganic chemistry.

EXPERT EXPANSION

Now the commission has revised its working procedures to open the PhEur up to the nomination of experts from non-PhEur member states and non-observer countries, a move that Keitel says will give the EDQM access to new experts as well as offering them the opportunity to help shape the PhEur in future.

In an interview with the Pink Sheet, she noted that the vast majority of active pharmaceutical ingredients (APIs) on the European market now originate from countries outside Europe and the US. “These are the manufacturers and experts that have the knowledge, so it would be a waste to limit it [the PhEur] to experts nominated by the European member states and not use expertise from around the world.”

She said that the decision to include more experts was in principle driven by the need to expand participation in the PhEur to more countries “but we always have specific needs in certain areas, always in the chemical field, and in the field of inorganics,” that the expansion could help to meet.

Following a revision of the PhEur’s terms of reference, there are now 58 groups that meet regularly two or three times a year, consisting of both permanent expert groups as well as working parties that are set up as the need arises, according to Keitel. As to how the numbers of experts might change following the decision to invite input from more countries, she said it was difficult to forecast: “Some groups will have more experts, and over the next three years we will also create more ad hoc working parties.”

NEW AREAS

A new working party has already been set up to deal with vibrational spectroscopy and analytical data modeling (VSADM), “and we have a working party on function-
ality-related characteristics of excipients – so we have some very specialized groups,” Keitel observed.

The VSADM initiative was triggered by the working party on process analytical technology (PAT) “which saw a specific area where we didn’t have expertise, so we set up a new one.”

The PhEur, she added, is also the first pharmacopoeia to include a general text on the application of chemometrics (carrying out calculations on measurements of chemical data) in analytical methods. “This is related to PAT where you don’t rely on end product testing any more but you generate data throughout the process.”

This is an important step, she said, because “it is the first time that any pharmacopeial guidance has been provided on this topic. We are proud of what we believe we have done in embracing these new technologies, because the pharmacopoeia can often be seen as something that is stifling innovation because you have legally binding standards. So this is in the context of embracing the concepts of quality by design, PAT, and so on. These texts are not legally binding but provide guidance and support to users.”

She said that she was “pretty sure” the other pharmacopoeias – mainly the United States Pharmacopeia (USP) and the Japanese Pharmacopoeia (JP) – would follow suit. “We have a tendency, if you see that your sister pharmacopoeia has developed something in a specific field, you often take this as a basis for your own. You may not end up with the same result, but you try not to reinvent the wheel.”

**WHICH PHARMACOPEIA TO USE?**

This also raises the question of how the pharmacopoeias co-exist across the world, and how countries choose which pharmacopoeia they want to provide their reference standards.

“The choice is related to the specific country’s regulatory system and legislation,” says Keitel. In Europe, the PhEur is legally binding, in Japan it is the JP. The situation in the US is different as the USP is non-governmental, “but normally the FDA applies USP standards.”

Other countries that have not developed their own pharmacopoeias decide which one(s) to use. For example, Keitel says, Canada and Australia have decided to accept the PhEur, the USP and the British Pharmacopoeia, “knowing very well that at least half of the BP is a reproduction of the PhEur.”

Where more than one pharmacopoeia is used, Keitel explains, it is up to the applicant to decide which one to refer to, but then they are bound by this decision. “So if, for example, you apply for a marketing authorization in Australia and decide to go for the PhEur, you always have to apply it. You cannot, in a case where a product does not meet the requirements of the PhEur, then say, hey, but there is a different monograph in the USP so I will use that one.”

**HARMONIZATION EFFORTS**

Clearly, though, it is in the interests of all concerned that the standards in the pharmacopoeias are aligned as far as possible. A harmonization initiative has been under way since 1989 in the form of the Pharmacopoeia Discussion Group, which can decide to harmonize monographs or chapters either retrospectively or prospectively, based on decisions of the expert bodies of each pharmacopoeia.

The group meets twice a year to discuss harmonization, on the basis of a continuously updated work program. The program focuses mainly on excipients, with most of the products on the agenda being proposed by industry associations or excipient manufacturers. “But we also harmonize general methods and it is clear that these are important because if think about chromatography, for example, this is used in every single monograph.”

And when the International Council on Harmonization decided to draft a guideline on the control of elemental impurities, they asked the pharmacopoeias to come up with a harmonized position “because it doesn’t make sense to have a harmonized ICH guideline and then have differences in the pharmacopoeias, so these are things that are high on the agenda.”

**BIOOTHERAPEUTICS**

These and other aspects will be discussed at the forthcoming international conference on the European Pharmacopoeia, which is taking place in Tallinn, Estonia, on Sept. 27-28, 2016. At the conference, a dedicated workshop will be held to discuss another evolving topic: how the PhEur should deal with biologicals and biosimilars.

Biotherapeutics have been a topic since the early 1970s, but “now with biosimilars and newer biotherapeutics there is a discussion on what the pharmacopoeias can contribute in this area, and what the monographs and general texts should cover,” says Keitel. “It is a continuous process, and it is important to reflect on the future of pharmacopoeias in the area of biotherapeutics.”

Other workshops at the conference will look at new technologies and their potential impact on monographs, the impact of the ICH Q3D guideline (elemental impurities), as well as excipients, other pharmaceutical components and current harmonization initiatives.

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