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Japan Price Reforms Will Be Pro-Innovation, Inclusive - Official

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Discussions at the health ministry's advisory Central Social Insurance Medical Council (Chuikyo) are now getting underway with a view to deciding the shape of actual reforms by the end of the year.

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Perhaps seeking to soothe fears that have been rising within the research-based pharma industry in Japan since new drug pricing reforms were outlined at the end of last year, Dr. Yasuhiro Suzuki, the director general of the Ministry of Health, Labour and Welfare's Health Insurance Bureau, told a recent conference in Tokyo that there is "no intention to move away from pro-innovation policies."

The most important factor in the reform discussions, set to take place over the course of this year, is "maximizing patients' benefits and value" he stressed, explaining that the government has to balance finite budget resources against rising spending on drugs under the country's national health insurance system.

"Pharma spending is now around JPY8.9tn [$79.92bn], accounting for around 25% of total health spending," Suzuki noted at the Biotechnology Innovation Organization's BIO Asia International Conference in Tokyo. Generics have been growing strongly, helped by prescribing fee and other policy incentives, and now account around half by volume of Japan's drug market, the aim being to raise this figure to 70% by mid-2017, he said.

But even so, a rapidly aging population - and the rise in overall healthcare spending that this is driving - means that there is a need "to strike a balance between innovation and sustainability, transparency, and predictability, and quality of care" in the reforms, Suzuki explained.

REFORM OUTLINE

At the end of last year, the powerful Council For Economic and Fiscal Policy under Prime Minister Shinzo Abe released a general roadmap for drug reimbursement pricing reforms that included a shift to the annual (rather than the current biennial) general revision of prices, based on an annual survey of actual market prices for all products.

Also among the preliminary recommendations was a quarterly review and repricing of drugs for which sales have increased above a certain amount due to new indications, and a possible revision of a price adjustment system for high priced drugs that takes into account prices in other selected reference countries.

There are also plans to ensure that the "innovation premium" system introduced on a trial basis several years ago, and which exempts eligible novel medicines from regular price cuts during their patent life, is used "appropriately".

The move over new indications was precipitated in large part by the explosive sales growth in Japan last year for **Ono Pharmaceutical Co. Ltd./Bristol-Myers Squibb Co.**'s cancer drug *Opdivo* (nivolumab) following the PD-1 inhibitor's launch in non-small cell lung cancer, but for which it retained the same high price it had been awarded for the much smaller initial indi-

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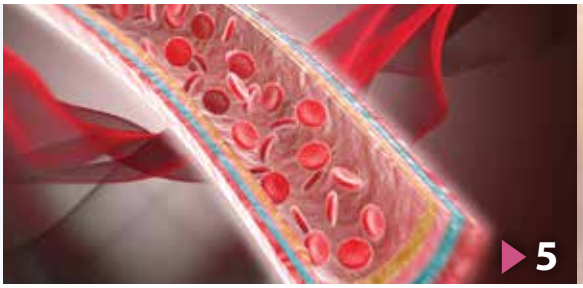

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Now What? Sanofi CEO Urges Incentives As China Embraces New Drugs

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Delinking drug approvals from price agreements, and providing timely and adequate reimbursement coverage, are just some of the policy changes top big pharma executives would like to see if China is to create an operating environment conducive to innovation.

Off-Label Opioid Promotion: US FDA 'Does Not Object' To Intranasal Deterrence Data, Egalet Says

https://pink.pharmamedtechbi.com/PS120347

In decision that reflects policy confluence of opioid abuse deterrence, off-label communications and marketing exclusivity, FDA will allow Egalet to distribute truthful, nonmisleading information about Arymo ER's intranasal abuse-deterrence data even though the long-acting opioid was blocked from receiving a labeling claim.

Inspection Delays Remain For Novel Approvals By US FDA; Will Quality Office Help?

https://pink.pharmamedtechbi.com/PS120348

Final assessment of the PDUFA V new drug review 'Program' flagged inspection delays as a continued sticking point for on-time approvals. US FDA says consolidation of manufacturing oversight under the agency's new quality office will help.

Accelerating Antibiotics: Kevin Outterson And Joe Larsen Explain CARB-X

https://pink.pharmamedtechbi.com/PS120349

Podcast with CARB-X Executive Director Kevin Outterson and BARDA Acting Deputy Director Joe Larsen describes the work of the accelerator, which just announced the first eleven projects in its portfolio.

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cation of malignant melanoma.

Discussions at the health ministry's advisory Central Social Insurance Medical Council (Chuikyo) are now getting underway with a view to deciding the shape of actual reforms by the end of the year, Suzuki told the BIO Asia session. Despite some concerns expressed by big pharma that the process may not be inclusive of all key stakeholders, Suzuki insisted that "we will discuss [the planned changes] with industry, patients and medical sector."

HTA, INDICATION PRICING

One clear theme to emerge from the official's comments at the conference was cost-effectiveness, and there are signs that the reforms may include a more routine requirement for applicants to analyze and demonstrate this for their new drugs.

Japan is already rolling out a pilot health technology assessment (HTA) scheme, but this is initially being applied only to a limited number of already approved products to retrospectively determine if the reimbursement prices awarded were appropriate.

"HTA can be used to help determine cost-effectiveness" and in future is also likely to be applied after product approvals, "so it will not delay the [regulatory] process" as in some other countries, Suzuki said. Current systems for the priority review and expedited approval of high-need drugs will also continue to apply.

Given the rising pressures on Japan's national health and drug budgets, "We want to shift resources to the most effective drugs. It is a matter of the composition of spending," the official explained.

The HTA evaluation process for medicines may actually result in some products having their prices increased, something that has already been stressed by Japan's Health Minister (Yasuhisa Shiozaki). Furthermore, the (downward) price adjustments for generics under the new annual review system may in fact be greater, due to the generally deeper discounting in this sector, Suzuki observed.

> One clear theme to emerge from comments at the conference was cost-effectiveness, and there are signs that the reforms may include a more routine requirement for applicants to analyze and demonstrate this for their new drugs.

While he was unable to elaborate given the still early stage of the reform discussions, the MHLW official said that indication-based pricing would be another of the options on the table this year. This would again seem to reflect the experience with Opdivo, which threw into sharp relief the lack of provisions for adjusting price according to patient population size.

US INDUSTRY'S CONCERNS

Speaking on behalf of the US research-based pharma industry association PhRMA, the group's Japan representative Amy Jackson told the same session that Japan's current pricing policies had been "very effective" in achieving government goals, such as increasing the number of R&D projects and clinical trials in Japan, and encouraging local investment.

In 2015, the local member companies of PhRMA the European industry federation EFPIA were sponsoring 825 trials in Japan, and this number had now increased to more than 1,000, she noted.

Despite the political and public concerns over rising drug spending, this is actually forecast to remain flat over the next five years, given existing cost controls, rising generic uptake, and the fact that median prices in Japan are actually lower than in the US and EU, something highlighted recently by **Pfizer Japan Inc.**, which warned over the possible impact on investment. *(Also see "Japan Pricing Reform Process Must Be Participative – Pfizer" - Pink Sheet, 9 Mar, 2017.)*

"We actually support greater generic uptake to provide [budget] headroom for innovation, but uptake remains slower than in many other major markets, and also many long-listed branded products are still on the market in Japan," Jackson observed.

Echoing Suzuki's comments that other aspects of health provision besides drugs (such as various medical fees) may also be examined to ensure systemic cost effectiveness, she added that "there is also a need to make reforms in the rest of the health system's spending to improve efficiency."

To help ensure appropriate medical use of specialist products in specific settings, Japan last year started a system of "optimal use" guidelines that has so far been applied to Opdivo and **Astellas Pharma Inc.**'s PCSK9 inhibitor for hypercholesterolemia *Repatha* (evolocumab).

INNOVATION ESSENTIAL

PhRMA's lackluster market sentiments were reflected in other comments made in a lunchtime "fireside chat" by **GlaxoSmithKline PLC**'s Japan country president Philippe Fauchet, who said the Japanese drug market was flat last year, and is forecast to remain so for the next four years. There has been an 8-9% fall in the first few months of this year, with some companies' sales down as much as 20%, he told the meeting.

"2021 will be equivalent to the 2016 market size. Generics are increasing, long-listed drugs are decreasing, so we must use innovation to grow," he observed. "Without innovation we have to face the reality of a declining market," which is creating a situation where the profitability of some less innovative local companies is already low and may even fall into the red.

From the editors of PharmAsia News.
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Industry Fears Realized As Japan Moves To Annual Price Cuts
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New Japan Price Cut Push Has Industry Worried
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US FDA First's RMAT Designation: Humacyte Got A 'Quick Response'

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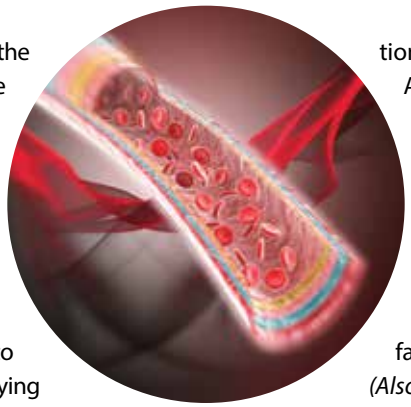

With the help of a quick response from the US FDA, **Humacyte Inc.** appears to have become the first company to receive a Regenerative Medicine Advanced Therapy (RMAT) designation from the agency for its investigational human acellular vessel *Humacyl*.

Although FDA is not able to explicitly confirm whether the RMAT designation was the first issued, Center for Biologics and Evaluation and Research (CBER) Director Peter Marks did point to Humacyte's March 20 announcement when testifying before the Senate HELP Committee March 21. Marks also authored an FDA Voice Blog post dated March 21 with the headline "This is Not a Test: RMAT Designation Goes Live," although the post did not mention Humacyte specifically.

"I think we have tried to move quickly on this, and we look forward to continuing to move forward," Marks said at the hearing. "And we are thankful for the legislation that has passed that has provided this pathway."

A Humacyte spokesperson tells the Pink Sheet that the company believes that it is the first to receive the designation, but that it isn't completely certain.

Similar to the breakthrough therapy designation, the RMAT designation allows for early and frequent communication between sponsors and FDA, and "will help reduce overall product development times," Marks noted in his blog post. Sponsors may also be eligible for priority review and accelerated approval.

The designation was created in the 21st Century Cures Act, and to qualify a product must meet the following criteria:

- It is a regenerative medicine therapy defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, except for those regulated solely under Section 361 of the Public Health Service Act and 21 CFR Part 1271
- It is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition; and
- It is indicated by preliminary clinical evidence to have the potential to address unmet medical needs for the disease or condition.

A RAT BY ANY OTHER NAME

Some experts have argued that the RMAT designation should be broadened to include gene therapies and other types of innovative treatments. *(Also see "Will US FDA User Fee Reauthorization Bring More RATS?" - Pink Sheet, 5 Mar, 2017.)*

And while FDA appears to have saved itself some awkwardness by changing the Congressionally specified term for the designation – the legislation had dubbed it Regenerative Advanced Therapy, or RAT – more substantive changes would require new legislation, which may be difficult to achieve under the increasingly raw atmosphere on Capitol Hill.

Frank Sasinowski, a director at Hyman, Phelps and McNamara, had suggested changing the acronym to ART (advanced regenerative therapy), arguing that Congress failed to consider the initial resulting acronym. *(Also see "Will US FDA User Fee Reauthorization Bring More RATS?" - Pink Sheet, 5 Mar, 2017.)*

A FAST PROCESS

At least in the initial rollout of the RMAT designation, FDA appears to be moving through the requests at a fast pace.

The Humacyte spokesman said the agency provided a "quick response" for the application.

"We believe this underscores the significant medical need for improvements in vascular access for patients with kidney failure requiring life-sustaining hemodialysis," the spokesman said. "This is a great new program FDA has provided for ground breaking new technologies like ours to have the potential to reach patients in need as fast as possible."

A bioengineered blood vessel, designed for the treatment of end-stage renal disease, Humacyl is a biologic and will be regulated by CBER, the company said. Humacyl is currently undergoing a 350-patient Phase III clinical trial, where it is being compared to an expanded polytetrafluoroethylene graft with kidney failure who are not candidates for fistula placement.

According to FDA, the request for an RMAT designation generally does not need to include the submission of primary data, but rather a description of the preliminary clinical evidence. The agency calls for an inclusion of "a brief description of any available therapies for the disease or condition, the study design, the population studied, and the endpoint(s) used; and a description of the study results and statistical analyses (e.g., subgroup analyses)."

The decision to pursue the designation was based on clinical data from Phase II studies of Humacyl, the company said. Humacyl demonstrated potential for long-term functional vascular patency, with only one infection attributed to the product. Expanded polytetrafluoroethylene grafts, conversely, are prone to thrombosis and infection, and may require multiple interventions or hospitalizations to remain functional.

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Ocrevus Launching Quickly Even After Manufacturing Worries Delayed US Approval

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Genentech Inc.'s multiple sclerosis therapy *Ocrevus* (ocrelizumab) will reach the US market in the next few weeks now that the **Roche** unit has overcome a regulatory hurdle that extended FDA's review process.

On March 28, FDA approved ocrelizumab, a CD20-directed cytolytic antibody, for the treatment of patients with relapsing or primary progressive forms of multiple sclerosis.

Ocrevus is the first drug approved in the US for primary progressive disease (PPMS), which accounts for approximately 15% of all MS cases. In the pivotal ORATORIO trial, ocrelizumab demonstrated significantly slower disability progression, as well as a reduction in brain lesion volume, compared with placebo. *(Also see "Roche's Ocrelizumab Poised To Seize Primary Progressive MS Opportunity" - Pink Sheet, 8 Oct, 2015.)*

"This therapy not only provides another treatment option for those with relapsing MS, but for the first time provides an approved therapy for those with primary progressive MS," Billy Dunn, director of FDA's Division of Neurology Products, said in a press release statement announcing the approval.

Ocrelizumab, which holds breakthrough therapy and fast track designation, was evaluated under a priority review and the original user fee goal date was in late December. However, the review period was extended by three months following Genentech's submission of additional data related to the drug's commercial manufacturing process. *(Also see "Roche's Highly Anticipated Ocrelizumab Delayed By Manufacturing Issues" - Pink Sheet, 20 Dec, 2016.)*

A Genentech spokesman said he could not comment on the additional information submitted to FDA.

However, with its approval coming on the reset user fee goal date, ocrelizumab did not fall victim to a complete response letter focused on manufacturing issues, which has become an increasingly common fate for both novel drugs and new formulations of older drugs. *(See the Pink Sheet Performance Tracker chart for a listing of recent complete response letter).*

Ocrevus will launch at a price of $65,000 per year.

PRICED BELOW OTHER MS THERAPIES

Ocrevus will be available to US patients within two weeks and will launch at a price of $65,000 per year, Genentech said.

The Ocrevus starting dose is a 300 mg intravenous infusion, followed two weeks later by another 300 mg infusion. Subsequent doses are 600 mg infusions every six months.

In a March 28 note, Salim Syed, a senior biotech analyst at Mizuho Securities USA, said the launch price represents a 25% discount to **EMD Serono Inc.**'s *Rebif* (interferon beta-1a) and a 20% discount to other MS therapies on average.

Ocrelizumab was studied against Rebif in the two pivotal Phase III studies – OPERA I and OPERA II – that supported approval for relapsing disease (RMS). In those studies, ocrelizumab significantly reduced the annualized relapse rate and the proportion of patients with disability progression confirmed at 12 weeks after onset compared to Rebif. *(Also see "Ocrelizumab May Represent Roche's Rebound In Neuroscience" - Pink Sheet, 30 Jun, 2015.)*

Despite the lower price point relative to comparators, the ocrelizumab launch price is higher than that which the Institute for Clinical and Economic Review has concluded would be considered cost effective. *(Also see "MS Drug Prices Far Exceed Value Thresholds, Even At Current Discounts – ICER Report" - Pink Sheet, 14 Feb, 2017.)*

INFUSION REACTIONS, INFECTIONS AND CANCER RISKS

Ocrelizumab enters the market with a relatively clean label; it lacks a boxed warning and Risk Evaluation and Mitigation Strategy, which have been required for other MS drugs, including **Biogen Inc.**'s integrin receptor antagonist *Tysabri* (natalizumab) and **Sanofi**'s CD-52 directed cytolytic monoclonal antibody *Lemtrada* (alemtuzumab).

The Warnings and Precautions section of Ocrevus labeling focuses on three main risks: infusion reactions, inflections and malignancies.

In MS clinical trials, 34%-40% of Ocrevus-treated patients experienced an infusion reaction even after receiving steroids or other pre-medication beforehand to reduce this risk. The highest incidence of reactions was with the first infusion. "There were no fatal infusion reactions, but 0.3% of Ocrevus-treated MS patients experienced infusion reactions that were serious, some requiring hospitalization," labeling states.

Labeling directs healthcare providers to pre-medicate patients with methylprednisolone, or an equivalent corticosteroid, and an antihistamine prior to each infusion. Patients should be monitored closely during, and for at least one hour after, infusion.

Infections have been a longstanding concern with ocrelizumab and the reason for its discontinued development in rheumatoid arthritis. *(Also see "Despite Ocrelizumab Infection Risk, Roche Sees Multiple Sclerosis Opportunity" - Pink Sheet, 23 Mar, 2010.)*

In the MS trials, infection rates were slightly higher in ocrelizumab-treated patients compared to Rebif-treated patients in the RMS studies or placebo-treated patients in the ORATORIO study in PPMS.

Ocrelizumab increased the risk for upper and lower respiratory tract, skin and herpes-related infections, labeling states, but was not associated with an increased risk of serious infections in MS patients.

Labeling includes a discussion of the potential risk of progressive multifocal leukoencephalopathy (PML).

PML, an opportunistic infection of the brain caused by the JC virus, has been reported with treatment with other anti-CD20 antibodies – including Genentech's *Rituxan* (rituximab), a precursor to ocrelizumab – and other MS therapies, such as Tysabri.

While noting that no cases of PML were identified in ocrelizumab clinical trials, labeling warns that "at the first sign or symptom suggestive of PML," healthcare providers should "withhold Ocrevus and perform an appropriate diagnostic evaluation."

Labeling also states that an increased risk of malignancy "may exist" with ocrelizumab.

"In controlled trials, malignancies, including breast cancer, occurred more frequently in Ocrevus-treated patients. Breast cancer occurred in six of 781 females treated with Ocrevus and none of 668 females treated with Rebif or placebo."

Genentech's postmarketing commitments include conducting long-term safety studies, a spokesman said. The company also is continuing to investigate long-term safety and efficacy in open-label trials.

> Labeling warns about the risk of PML even though no cases of the brain infection were identified in ocrelizumab clinical trials.

ANOTHER BIOLOGIC WITHOUT A SUFFIX

Ocrelizumab becomes the fourth novel biologic approved this year in apparent contravention of FDA's final nonproprietary naming policy for biological products.

In a final guidance released Jan. 12, FDA stood by its earlier proposal to give distinguishable, four-letter suffixes to the nonproprietary name of all biosimilars and new biologics, and to retrospectively add suffixes to the names of previously approved products. *(Also see "Biologic Product Naming: US FDA Sticks With Suffixes 'Devoid Of Meaning'" - Pink Sheet, 12 Jan, 2017.)*

However, the agency has yet to apply the naming policy to novel products upon licensure.

Valeant Pharmaceuticals International Inc.'s psoriasis treatment *Siliq* (brodalumab) was the first novel biologic approval following the guidance's release. At the time, FDA said the product was approved without a suffix because the agency did not want to delay it from reaching market. *(Also see "Where's The Suffix? Valeant's Siliq Approved Without Four-Letter Identifier" - Pink Sheet, 16 Feb, 2017.)*

However, the agency also appears be waiting for Office of Management and Budget approval of the information collection under the final guidance before imposing the suffix requirement for novel products. *(Also see "FDA's Burden Estimate On Biologic Naming Ignores Downstream Costs, Critics Say" - Pink Sheet, 16 Feb, 2017.)*

In addition to ocrelizumab, two other novel biologics have been approved without a distinguishable suffix in the past week: **Pfizer Inc.**'s PD-L1 inhibitor *Bavencio* (avelumab) for Merkel cell carcinoma, and Sanofi and **Regeneron Pharmaceuticals Inc.**'s IL-4/IL-13 inhibitor *Dupixent* (dupilumab) for atopic dermatitis.

Published online March 29, 2017

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Roche Set For Disruptive Entry To MS Market With 'Brave' Ocrevus Pricing Strategy
http://bit.ly/2nom87L

US FDA And OMB Should 'Pause' Billion-Dollar Quality Metrics Program, Industry Groups Say

JOANNE EGLOVITCH joanne.eglovitch@informa.com

Pharmaceutical industry groups are calling on FDA to hit the "pause" button on the latest iteration of its quality metrics initiative due to concerns about high cost and low benefit.

The recommendation was made by a variety of groups representing brand, generic and ingredient companies, commenting both individually and in an industry coalition. One, the Association for Accessible Medicines representing generic makers, estimated that the initiative could cost industry $1bn per year to comply with the initiative as set forth in revised draft guidance, and it also asked the White House Office of Management and Budget to disapprove it.

That argument could resonate with anti-regulatory stance of President Trump's OMB, which will help carry out an executive order requiring elimination of two regulations for every new one issued, at least for "significant regulations" like industry groups say the quality metrics initiative would be. *(Also see "US FDA Likely Not 'Significant', Could Be Mostly Spared From Trump's Regulation-Slashing Order" - Pink Sheet, 10 Feb, 2017.)*

Pharmaceutical industry groups said the quality metrics initiative could even have the unintended consequence of causing the very drug shortages it is designed to prevent.

Some groups added that a lack of uniform definitions continues to bedevil the program. They're urging FDA to start with a scaled back effort to work on questions like what would constitute "invalidated out-of-specification results" or "saleable units."

FDA ENVISIONS PREDICTING SHORTAGES AND GRANTING RELIEF

FDA proposed the quality metrics program after enactment of the FDA Safety and Innovation Act (FDASIA) of 2012 to get a better handle on how manufacturers are addressing quality, and to set better benchmarks for measuring quality. Two provisions of FDASIA gave FDA tools to improve its approach to regulating drug quality: Section 705 (risk-based inspections) and Section 706 (FDA access to records). Together, they gave FDA the authority to collect and process information on production processes and to use that data to improve quality and avert drug shortages.

FDA said that participation offers the promise of potentially getting inspected with less frequency and being subject to less stringent change control requirements. FDA officials are urging full participation in its quality metrics program once an electronic portal goes live Jan. 1. They say that without this participation the program will not succeed, the agency will not have enough information to predict drug shortages and the industry will not see regulatory relief. *(Also see "FDA Urges Full Participation In Quality Metrics Program" - Pink Sheet, 24 Feb, 2017.)*

In November, FDA issued revised draft guidance on a pilot program to collect pharmaceutical manufacturers. The revised draft was stripped of a mandatory reporting requirement, quality culture metrics and an on-time product review metric, and FDA no longer insists on product metrics, allowing a site metric alternative. *(Also see "FDA's Revised Quality Metrics Program: Voluntary Now, Mandatory Later" - Pink Sheet, 27 Nov, 2016.)*

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Pharmaceutical industry groups said the quality metrics initiative could even have the unintended consequence of causing the very drug shortages it is designed to prevent.

Originally the deadline for public comment was Jan. 27 but the agency Jan. 9 extended the deadline by two months, to March 27, in response to requests for an extension to allow additional time to submit comments.

The agency received several dozen comments on the revised draft. Although respondents acknowledged the agency's response to concerns raised previously, most went on to raise serious reservations about the program. The comment from the International Society for Pharmaceutical Engineering reflected a consensus view: "that the program, based on our analysis, as proposed has low or no value and the burden is substantial."

COALITION SAYS PROGRAM SHOULD BE 'PAUSED'

The Cross-Industry Quality Metrics Collaboration Group said in its March 27 comments that "after careful deliberation and analysis, the Collaboration Group believes that FDA's metrics collection proposal should be paused and there needs to be further public dialogue between industry and FDA. … We believe the that the burden of FDA metrics collection far outweighs the benefits, as

least as currently proposed."

The coalition is a broad informal group across the pharmaceutical industry and includes ISPE, the Association for Accessible Medicines (formerly the Generic Pharmaceutical Association); the Active Pharmaceutical Ingredients Committee; the Bulk Pharmaceuticals Task Force; the Pharma & Biopharma Outsourcing Association and the Pharmaceutical Research and Manufacturers of America.

The coalition further noted that "as we have continued to learn in depth about what it would take to operationalize a metrics program of the kind proposed by FDA, we have concluded that such a program would require substantial resources, present significant operational challenges and complexities, and draw resources and management attention away from other programs that drive continual quality improvement."

Coalition members separately filed similar comments.

For example, PhRMA asked for FDA to "pause" its quality metrics initiative for further dialogue with industry. While acknowledging that there has already been a lot of dialogue, PhRMA said, "we now believe that the burden and timing of both industry and FDA collecting company-submitted quality metrics data outweighs the stated potential benefits to the extent that we do not support the program moving forward as currently proposed without further dialogue."

REPORTERS LIST OPPOSED

Many of the respondents also did not support a proposed "reporters list."

FDA's revised draft guidance calls for the agency to publish a list of quality metrics reporters, which it views as an incentive. Companies that report all metrics on their products will appear on a "top tier" list. Reporting some metrics on their products puts them on a mid-tier list and just reporting the site data would put them on a lower-tier list. *(Also see "FDA's Revised Quality Metrics Program: Voluntary Now, Mandatory Later" - Pink Sheet, 27 Nov, 2016.)*

AAM decried the reporters list, saying it "is ill-advised, potentially misleading, and converts a purportedly voluntary program into a mandatory one in violation of federal law."

The association for generic drugs and biosimilars went on to say that, "as FDA itself acknowledges, the reporters list would provide no relevant information about a company's compliance with current GMPs or other quality requirements. Nevertheless, it is structured to misleadingly suggest that companies listed as 'top tier' site reporters have a stronger quality program than companies listed as "mid-tier" or that are not on the list at all. … Because the reporters list is intended to exert significant pressure on companies to participate in the program, it transforms a voluntary program into a mandatory one. FDA, however, does not have statutory authority to impose a mandatory quality metrics reporting program via guidance."

OMB ASKED TO DISAPPROVE PROGRAM

AAM went on take the unusual step of filing additional comments on the draft guidance with the FDA desk officer at the Office of Information and Regulatory Affairs in the White House's Office of Management and Budget setting forth its contention that FDA has significantly underestimated the cost of complying with its proposed quality metrics guidance.

In those comments, the association argued that FDA doesn't need quality metrics data to do its job, that no statute or court order mandates or authorizes the collection of quality metrics data, and that therefore OMB has a statutory obligation to independently assess the necessity of the agency's proposed information collection.

Arguing that the proposed collection of quality metrics data "is unusually burdensome and unnecessary under the Paperwork Reduction Act of 1995," the association said it "respectfully urges OMB to disapprove it."

COMPLIANCE COULD COST $1BN PER YEAR

AAM asserted in its comments to FDA and OMB that complying with the proposed guidance it's calling a "substantive rule" would cost the pharmaceutical industry as much as $1bn a year – far exceeding the $100 million per year threshold for significant regulations.

AAM estimates that the ongoing burden associated with collecting and maintaining quality metrics data in the form and format required by the draft guidance will range from $107m to $478m a year more than FDA had estimated.

The agency's cost estimates "improperly excludes one-time implementation costs, such as capital costs associated with creating and upgrading data system, creating new quality metrics policies, employee training and re-negotiating quality agreements with manufacturing partners to require reporting of quality metrics data."

The association estimated that the economic impact of FDA's proposals, including one-time and ongoing burdens, "will range from a low of $934m to a high of $1.77bn. This includes a recurring annual burden estimated to range between $635m and $1bn as well as a one-time cost to industry of $299m to $766m to establish infrastructure and policies to implement the metrics program."

AAM concluded that "the costs associated with complying with the draft directive are significant and perpetual, they will require the creation of infrastructures for managing and reporting data that will require continuous maintenance, increased staffing, additional contract fees and renegotiation of quality agreements."

DRUG SHORTAGES COULD RESULT

Industry also said that cost of participating in the program and collecting the metrics would be prohibitive and could, ironically, lead to the drug shortages that the program is trying to prevent.

Teva Pharmaceutical Industries Ltd. said that "the revised draft guidance underestimates the burden on industry, particularly those segments of industry with complex and extensive supply chains, and underestimates the subsequent burden to FDA, because of the vast quantity of data that establishments would be required to collect and submit under the proposed quality metric program. These burdensome reporting requirements could increase the potential for drug shortages because some companies may make choices based on FDA metrics to the detriment of the drug supply by discontinuing products, increasing drug prices, or diverting resources from other quality activities."

PILOT NEEDS STANDARD DEFINITIONS

ISPE said that one problem is that many of the terms and definitions of data elements in the guidance such as "saleable unit" and "invalidated out-of-specification results" are different from those commonly used in industry and are also open to interpretation from site to site.

Additionally, the society said that "lack of clear and standardized quality metrics data elements will confound attempts at data analysis and will likely lead to unusable data. This will limit the ability to draw conclusions and achieved the desired benefits."

ISPE added that "the lack of clarity on definitions is especially problematic for CMOs [contract manufacturing organizations] who could be requested to structure data differently for each of their clients. A senior leader from a CMO has said that we 'need better clarity on definitions, otherwise we will be requested to provide data the way each sponsor has structured it.'"

Until these issues are resolved, this program can lead to "inappropriate allocation of resources to a relatively low value program which subtracts from existing KPI (key performance indicators) and continual improvement programs which have been designed to have value for a site or company and high level of management attention distracting from other activities that offer more perceived value."

PDA also commented that there is the potential that data could be used inappropriately to compare results from one plant to another, rather than to foresee future trends.

"PDA would like to emphasize that the FDA consider the importance of the trends of each of the calculated metrics rather than compare individual results from one plant site or one company to another. … Because of the great diversity across manufacturing operations and product types, a straight comparison of data points may not provide valuable or operational information for the risk-based model of inspections."

TIMELINES QUESTIONED

AAM also said that the agency's proposed timeline for implementing the program is not reasonable. "Although the agency states that it does not intend to begin collecting quality metrics data until early 2018, the data it intends to collect would be from 2017. That means that in order to participate in the program, companies need to begin collecting and preparing the data now, even before the agency has addressed industry questions on the revised draft guidance. In other words, companies must pull the trigger before they have a clear target at which to aim. This 'ready, fire, aim' approach, however, is not reasonable."

"AAM believes that the program remains overly burdensome both to industry and to the agency and that the agency is still significantly underestimating those burdens. For example, to make product reports, many companies will need to collect and harmonize the data and information across different data platforms, companies and countries … in other words the program will be highly disruptive and expensive for many companies."

ISPE said that one problem is that many of the terms and definitions of data elements in the guidance such as "saleable unit" and "invalidated out-of-specification results" are different from those commonly used in industry and are also open to interpretation from site to site.

The Biotechnology Innovation Organization concurred and said there was insufficient time for companies to get data systems up and running. "BIO acknowledges that as this is an initial voluntary phase, it is likely that the companies that choose to participate will be the ones that have systems already in place that will allow submission of the requested metrics data. However, if FDA intends to open the electronic portal in January 2018 and expects to publish the notice with instructions and dates no fewer than 30 days prior to opening, time is short on finalizing the processes companies need to follow and what exact information will need to be collected."

REDUCED SCALE URGED

ISPE urged FDA to scale back its proposed quality metrics program until it gets a better handle on some of the challenges, recommending that "FDA voluntary program be conducted as a limited pilot and be further simplified and carefully structured to be more focused on desired objectives and benefits. Such simplification would clarify the program, reduce the burden and so encourage more participation in this phase giving a greater opportunity to realize benefits and provide learning."

Teva concurred. "We suggest that before launching an industry-wide program with a significant burden and uncertain benefits, FDA should analyze available site data, such as recalls, field alert reports and inspection observations with and without the addition of quality metrics submitted by a small group of participants in order to determine whether the benefit of submitting these data outweighs the use of currently available compliance data alone."

Whether paused or scaled down, one thing is for sure: FDA's quality metrics initiative will continue to be a hot topic in the pharmaceutical industry.

From the editors of Gold Sheet. Published online March 29, 2017

It's Time To 'Get Moving' To Meet ICH Q3D Deadline, Industry Told

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Manufacturers that have yet to begin compiling risk assessments to bring existing drug products into compliance with the International Council on Harmonization's Q3D elemental impurities guideline better get busy as the deadline to complete the assessments is fast approaching, a leading industry expert on the topic warned last week.

Nancy Lewen, an analytical chemist with **Bristol-Myers Squibb Co.** also gave some tips March 23 on overcoming obstacles in complying with ICH Q3D at the 3rd Annual Conference on Advancing Product Quality, sponsored by the Product Quality Research Institute and FDA in Rockville, Md. She said robust risk assessments can help manufacturers manage changes better so they don't have to default to automatic full testing on products.

The ICH Q3D guideline for elemental impurities, published in December 2014, sets permitted dally exposure (PDE) limits for 24 elements. The guideline takes effect in January 2018 for legacy products in the US, the EU and Japan; it has been in effect since June 2016 for new drug products in the US and Europe.

"If you are in the category where you are just beginning to be aware of things and trying to figure out what to do, even though we are coming quickly to the deadline, you still have time but you need to get moving," Lewen said.

ICH Q3D incorporates a risk-based approach to assessing the presence of elemental impurities in drug products. For example, manufacturers must quantify the risk of metals that reach the final product from container closure systems, excipients, drug substances, water and equipment.

RISK ASSESSMENTS SHOULD TELL STORY

She said the risk assessments should be living documents and should "tell a story" as well as have enough information to support their conclusions. Pharmaceutical manufacturers at a recent workshop said that the more difficult task in complying with the ICH Q3D guideline is conducting the risk assessments rather than testing for elemental impurities *(Also see "Pharmaceutical Manufacturers Grapple With ICH Q3D Implementation" - Pink Sheet, 13 Dec, 2016.)*.

The key to effective risk assessments is to "go back to the beginning and know and understand all aspects the manufacturing process," Lewen said.

She said it is important to ask these questions in developing risk assessments:

- How is your API made? What are the raw materials and the catalysts used?
- What are your excipients? Are they naturally sourced or mined?
- What type of processing equipment is used?
- What is the quality of the water used?

Lewen said one challenge is that good information on excipients may not be available, especially if they are naturally mined or sourced. She described an example of receiving separate batches of materials sourced from different parts of a mine.

"It is not always possible to homogenize a mine so the elemental impurities may or may not be present in that mine. These materials can be very different from batch to batch depending on the location in the mine. … So keep that in mind when you are doing a risk assessment," she said.

For manufacturers that use these excipients, it may be necessary to collect more data and possibly conduct full testing on the final product.

Lewen said vendors' ingredient changes are another challenge, and where robust risk assessments can help. "If you have a vendor that used to use palladium as a catalyst and now they have found a way to make something that they don't have to use a catalyst at all, then you might be able to take palladium off your list. Likewise, if something gets added, you may have to add it to your list. But you don't know until you use a risk-based approach and look at everything. Don't just jump to test. Understand your process."

She said risk assessments should also be able to help in managing changes in vendors. "Talk to your vendors and ask whether there are differences in how they make materials. You may or may not need to do

testing. The key is to be informed about your product and that is from your risk assessment."

CONSORTIUM'S EXCIPIENT DATABASE CAN HELP

Another challenge is vendors that refuse to provide information on their excipients. To deal with this, Lewen said that manufacturers can conduct their own searches in the published literature to gauge risk. Or they can use a database on excipients being developed by the Elemental Impurities Pharma Consortium that will soon be publicly available *(Also see "Drug Makers Urged To Collect Own Excipient Metals Data To Comply With ICH Q3D" - Pink Sheet, 20 Dec, 2016.)*. The database organizers said it will help reduce the burden of testing excipients that have already been tested.

The database is "starting to gain momentum" she said. Currently it is available only to manufacturers that donated materials to the database.

Lewen said the burden and cost of conducting these risk assessments will yield benefits down the road. She said through these risk assessments, "you will have greater knowledge about your process. … You will be able to identify potential problems before they become bigger problems."

Having these risk assessments will also ease the process of doing tech transfers because there is a set template for analytical testing.

"At BMS we have a set process and a set template for every tech transfer. The main difference is just different materials but the validation requirements and all those things are the same so it has made our life a lot easier in the analytical laboratory," Lewen said.

She said understanding the process and qualifying the risk also means having "significantly fewer discussions with toxicologists."

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

EMA Expanding Use Of Early Background Summaries To Support Initial Drug Evaluations

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The European Medicines Agency is planning to improve and expand the use of the "early background summaries" that its product team prepares to help the agency's scientific committees evaluate certain marketing authorization applications (MAAs).

Early background summaries were introduced towards the end of 2014 as part of a pilot project that ended last year. These documents provide the EMA's scientific committees with "regulatory intelligence analysis" on certain products that they are evaluating, alerting them as to whether further regulatory and/or legal advice may be required and whether the EMA needs to gather further information. "This could trigger any additional input that the rapporteurs deem useful," including, for example, "exchange with regulatory bodies outside the EU," the agency told the *Pink Sheet*.

Under the pilot, the EMA's product team prepared the summaries for use by the rapporteurs in various agency committees – the human medicines evaluation committee (the CHMP), the Pharmacovigilance Risk Assessment Committee and, where relevant, the Committee for Advanced Therapies – at Day 10 of the evaluation of initial MAAs.

MAAs were selected based on criteria such as: the legal complexities involved; the type of marketing authorization being sought; the type of product under evaluation; the disease being targeted in view of recent regulatory or scientific developments such as a clinical guideline under revision or development, previous evaluation in the same class or indication; scientific advice for other related drugs/indications; and new/evolving consensus in the disease field.

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Based on positive feedback from the pilot, the EMA said it was working with representatives from the CHMP, PRAC and CAT to expand the use of these documents as a Day 10 step within the evaluation of initial MAAs. It is also expanding the criteria used to select products for which background summaries will be prepared.

The overall feedback on 21 MAAs that were included in the pilot suggested that early background summaries "should be continued with certain adaptations" and that the criteria for prioritizing procedures that qualify for such summaries should be further elaborated.

Early background summaries are helpful for rapporteurs as they offer a critical background of the product being evaluated and provide information that may be of particular relevance to the application concerned, the EMA explained. In particular, the EMA's product team highlights regulatory and procedural aspects of the application and provides comments on the product information.

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Singapore Eye Wash Maker Blinks At US FDA's OTC Monograph, GMPs

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Emergency eye wash products made by a Singapore firm and distributed to US workplaces are noncompliant with FDA's OTC monograph for ophthalmic drug products, the agency says in a warning letter.

The warning FDA published March 28 followed an inspection at Opto-Pharm Pte Ltd.'s facility in Singapore during March 2016, when agency officials also found good manufacturing practices violations including failing to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, such as the purified water in the firm's eye wash products.

The letter submitted March 16 to Opto-Pharm states that that the firm's "Buffered Eye & Skin" products – distributed in the US under the *Xpect* and *First Aid Direct* brands by Cintas Corp. – are not labeled or formulated in accordance with the final ophthalmic drug products monograph.

The labeled indications state that the products are intended for flushing the eye and the product name "Buffered Eye & Skin" suggest that the products are intended for flushing the eye and skin, but flushing the skin is not a permitted indication in the final monograph for eyewash drug products.

FDA added that its not aware of sufficient evidence to show the products, as formulated and labeled, are generally recognized as safe and effective, the threshold for monograph compliance, and that the products have not been approved through applications submitted to the agency, rendering them unapproved new drugs marketed illegally in the US.

According to labeling listed in the National Library of Medicine database, Opto-Pharm makes the products for Cintas, the Mason, Ohio-based firm that supplies uniforms, facility services and first aid and other products for business workplaces around the US.

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> FDA warnings to manufacturers in Asian countries and other international markets are not uncommon, but warnings about nonprescription drugs are seen much less.

The Singapore firm also makes a product with same "sterile isotonic buffer solution" formulation as Xpect and First Aid Direct, but labeled only as an eye wash and distributed by Cintas subsidiaries Respond Industries Inc. and American First Aid Co., the NLM database indicates.

LEAKING CONTAINERS, SUSPECT EXPIRATION DATES

FDA warnings to manufacturers in Asian countries and other international markets are not uncommon, but warnings about nonprescription drugs are much less common and a warning specifically about noncompliance with agency regulations for eye wash products is practically unheard of.

The Opto-Pharm warning says the firm received customer complaints about leaking containers after shipping batches of products manufactured during periods when "numerous leaking containers and other bottle formation defects" were documented.

In addition to failing to prevent shipments after finding "numerous critical container-closure defects" during production, Opto-Pharm was re-using production-line components that are intended for single use, FDA says.

"Repeated use and re-sterilization can compromise [the equipment's] efficacy and physical/chemical stability (e.g., particles, leachables, extractables)," the letter states.

The firm "committed to develop and execute protocols for process performance qualification and equipment qualification," and in the warning letter FDA asked it to provide validation protocols and studies that evaluate whether its equipment is reliable, including determining whether the "process reproducibly yields an integral container-closure system."

A second GMP violation turned up during the inspection was failing to establish the reliability of Opto-Pharm's container-closure supplier's analyses through appropriate validation of its test results at appropriate intervals. The firm accepted values reported on the supplier's certificate of analysis without verifying the reliability of the results.

Opto-Pharm said it would send samples from the container-closure supplier to an external laboratory for density testing and periodically evaluate the supplier, however, in the warning FDA advised the firm that it should provide justification to demonstrate its specifications are appropriate for the drug products it manufactures.

Opto-Pharma also slipped on GMP compliance by failing to ensure its products bore an expiration date supported by appropriate stability testing, specifically for buffered saline and ophthalmic solutions it made in 2014 and 2015, and by failing during the inspection to provide raw data to support test results from stability studies it conducted for other products.

The warning states that "failure to conduct stability studies and lack of data supporting expiration dates compromises" detecting quality problems with marketed ophthalmic products, and that multiple customer complaints of leaking ophthalmic containers also calls into question the firm's ability to maintain sterility of its ophthalmic products throughout their labeled expiration dates.

"Without stability data, you cannot assure the quality of your products throughout their labeled shelf lives," FDA says in the letter.

Opto-Pharm committed to stability studies on its buffered saline and other products, but did not provide raw stability data for the other products. FDA asked the firm for raw stability data, within expiry, for all its ophthalmic products manufactured for the US distribution; antimicrobial effectiveness testing that evaluates whether its products contain a suitable preservative system; and an evaluation of whether it products' preservative systems remain effective at their expiration dates.

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Alka-Seltzer Antacid Will 'Plop, Plop Fizz, Fizz' Without Aspirin

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Original *Alka-Seltzer* pioneered offering an effervescent remedy for acid indigestion and pain and the iconic OTC brand looks to be the first in the category to reformulate without its analgesic component, aspirin, partly due to a risk of serious bleeding.

In advance of an FDA advisory panel meeting April 4 on the safety of antacid/aspirin products available under an OTC monograph, **Bayer AG**'s consumer products business announced it is bowing to winds of change and is reformulating the product marketed since 1931, along the way establishing "plop, plop, fizz, fizz" as an iconic advertising tag line.

The brand remained on the market over those decades despite competition that frequently grew and despite FDA requiring label warnings about potential liver damage from drinking alcohol while using products containing aspirin, related compounds and nonsteroidal anti-inflammatory drugs in 1998 and about the risk of serious bleeding from antacid/aspirin products in 2010.

In addition to helping prevent potential misuse of three Alka-Seltzer products that contain aspirin for pain relief and sodium bicarbonate and citric acid for acid indigestion, Bayer Consumer Health says it is reformulating the products because consumers are moving to single-indication products to remedy common conditions.

The pain relief indication will be removed from the labels with aspirin removed from the Alka-Seltzer antacid products – original, lemon-lime and extra-strength versions, which combine as the top-selling antacid/analgesic brand in the US *(see table)*.

"We see consumer purchase trends moving more and more in the direction of [products] that are focused solely on heartburn and the relief of stomach upset," said Andre Schmidt, US medical affairs vice president for Bayer Consumer Health, on March 23.

> Bayer contacted FDA, prior to the agency's advisory panel announcement, about reformulating and relabeling the three Alka-Seltzer products and says the change is not in response to the meeting, but follows the firm's own risk/benefit review and consumer preference tracking.

"Given the shift in consumer trends and consumer preferences and as well we eliminate any potential misuse that might happen with these combination products, we made the decision to reformulate certain Alka-Seltzer effervescent products," Schmidt, a physician, said in an exclusive interview about the change.

Bayer HealthCare LLC, which includes Bayer Consumer, says it is conducting stability tests of the new formulation and it has not started manufacturing. Reformulating and producing distribution inventory of an OTC monograph product should require one to two years, the firm says.

The existing antacid/aspirin Alka-Seltzer products will remain available during the reformulation, though the firm says it has advised distributors, retailers and other businesses that market or sell the brand that it will replace the current products.

Alka-Seltzer's history as the first effervescent antacid/aspirin for acid indigestion and pain relief includes decades of advertising featuring "Speedy" the cartoon character and sales in pharmacies and other venues from single-dose dispensing machines.

Packaging and labels for Alka-Seltzer antacid, in original, lemon-lime and extra-strength versions, will omit aspirin as an ingredient and pain relief as an indication following Bayer Consumer Health's reformulation.

Fizzing At Top Of Antacid/Analgesic Category

While competition grows from single-ingredient antacid products, Alka-Seltzer dominates the antacid/analgesic combination category, according to market research firm IRI's sales data from sales at supermarket, drugstore and mass merchandise chains, military commissaries and some club and discount chains. Chicago-based IRI's data cover the 52 weeks ending Feb. 19.

US ANTACID/ANALGESIC COMBINATION PRODUCT SALES BY BRAND	SALES	% CHANGE FROM YEAR AGO	MARKET SHARE	% CHANGE FROM YEAR AGO
Total	**$53.1m**	**(4.11)**	--	--
Alka Seltzer	$45.4m	(3.58)	85.59	0.47
Private label	$7.6m	(6.62)	14.27	(0.38)
Handy Solutions	$27,311	(57.25)	0.05	(0.06)
Family Care	$20,384	(7.59)	0.04	(0.00)
Convenience Valet	$14,183	(40.24)	0.03	(0.02)
Lil Drugstore	$9,306	(5.63)	0.02	(0.00)

Other antacid/aspirin products marketed for acid indigestion and pain include numerous private label/store brands as well as Tower Laboratories Inc.'s *Bromo Seltzer* and Navarro Discount Pharmacies LLC's *Vida Mia Pain Relief*.

ALL BAYER ANTACIDS WILL BE SINGLE-INGREDIENT

The reformulation is limited to the three Alka-Seltzer effervescent tablet products indicated for gastric symptoms and headache or body ache from causes including overindulgence in food or alcohol.

Products in the brand's *Alka-Seltzer Plus* line of effervescent tablets and capsules for cough/cold, congestion and sinus relief do not contain aspirin and are not being reformulated. Each of those contains acetaminophen and also combinations of dextromethorphan, guaifenesin, phenylephrine, doxylamine succinate or chlorpheniramine maleate.

Formulations also will remain the same for Alka-Seltzer brand chewables for heartburn (calcium carbonate) or gas and heartburn (calcium carbonate/simethicone) relief and a gummy-format calcium supplement for heartburn.

The chewables and the gummy, Schmidt says, compete directly with other antacid brands that for three of four years ago have showed "a consistent trend" of taking the single-ingredient approach.

"We just see that the consumer asks more and more for these types of products and not the combination products," he said.

Removing aspirin from the antacid effervescent tablets and the pain relief indication from their labels " is very much in line with the rest of the Alka-Seltzer family of products," Schmidt added.

BAYER ALSO REVIEWS RISK/BENEFIT PROFILE

Schmidt acknowledged that FDA is concerned about the safety of antacid/aspirin combinations. Before scheduling an advisory panel to consider whether the formulations and other OTC nonsteroidal anti-inflammatory drugs and acetaminophen

products should remain available under an OTC monograph, the agency in June 2016 published a Drug Safety Communication stating that the use of the products indicated to treat heartburn, sour stomach, acid indigestion or upset stomach is associated with internal bleeding.

Schmidt said Bayer contacted FDA, prior to the agency's advisory panel announcement, about reformulating and relabeling the three Alka-Seltzer products and the change is not in response to the meeting, but follows Bayer's own product risk-benefit review and its consumer preference tracking.

The firm is not aware what FDA's panel, in a joint meeting of the Nonprescription Drugs and Drug Safety and Risk Management advisory committees, will specifically discuss or what if anything the agency will require.

"We obviously knew that the FDA is continually looking at how to improve the monograph. That was certainly also the reason why we looked into the product, together with the change in consumer trends. We just took the decision that it's a good time point right now to make this decision," Schmidt said.

FDA's Center for Drug Evaluation and Research on March 3 said it continues to receive reports of internal bleeding potentially linked to use of antacid/aspirin products, including reports of patients requiring blood transfusions, despite requiring a warning statement about the risk of serious bleeding, including in the stomach and gastrointestinal tract, in the combination products' Drug Facts labels since 2010 and since its 2016 Drug Safety Communication. *(Also see "Safety Review For Upset Stomach, Hangover OTCs Reconsiders Science" - Pink Sheet, 7 Mar, 2017.)*

Schmidt said Bayer contacted FDA, prior to the agency's advisory panel announcement, about reformulating and relabeling and the changes follows Bayer's own product risk-benefit review and consumer preference tracking.

Antacid/aspirin products are among the OTCs containing acetaminophen or NSAIDs that were required to add a label warning on a risk of serious bleeding in a 2009 rule amending the OTC monograph for internal analgesics, antipyretics and antirheumatics, going beyond changes the agency proposed in a 2006 tentative final rule. The proposed guidelines included clearly highlighting the presence of acetaminophen in a drug and identifying ingredients as NSAIDs – ibuprofen, naproxen and ketoprofen in addition to aspirin. But the final rule added revised warnings against the use of multiple acetaminophen products and concurrent use of acetaminophen and the Rx anticoagulant warfarin. *(Also see "FDA Expands Acetaminophen, NSAID Labeling Beyond Tentative Final Rule" - Pink Sheet, 4 May, 2009.)*

CDER opened a docket – FDA-2017-N-0965 – for public comment on the NDAC/DSRAM joint meeting at the Tommy Douglas Conference Center in Silver Spring, Md., and will accept comments through April 3; comments received by March 21 will be provided to the committees and others will be considered the agency.

The gastrointestinal OTCs that will be discussed are for conditions such as heartburn, nausea, fullness, belching, gas, acid indigestion or sour stomach and are marketed under FDA's internal analgesic and antacid monographs and the nonprescription products indicated for hangovers on the meeting agenda are available under the overindulgence, internal analgesic and stimulant monographs. Through March 24, FDA had not published the committees' rosters, questions they will consider and other agenda details for the meeting.

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OTC Monograph Reform, User Fee Legislation Coming 'Any Day' – CHPA

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Legislation with proposals that drug firms were hesitant to get behind – reforming FDA's OTC drug monograph program and establishing a user fee program to support the agency's work – is close to surfacing in Congress with the industry's backing.

A separate change also requiring legislation but that the industry has backed from the start, eliminating the Affordable Care Act requirement that consumers have prescriptions to buy OTC drugs with flexible spending, health savings and other pre-tax accounts, took a backward step as the House cancelled a vote on legislation to repeal the act.

Consumer Healthcare Products Association President and CEO Scott Melville discussed the trade group's legislative priorities at the association's Annual Executive Conference in Amelia Island, Fla., on March 21.

Melville said CHPA expects a bill will be introduced to Congress "any day now."

"While optimistic about the prospects for it happening, we have more options to think about the innovations that can be unleashed once reforms are enacted," he said, adding that monograph reform is a "once-in-a-lifetime initiative."

FDA in 2014 launched an initiative to improve and modernize the OTC monograph system, opening a docket for comments and conducting a public hearing to solicit feedback on making the process "more agile and responsive." *(Also see "FDA Floats OTC Monograph Overhaul To Be "More Agile And Responsive"" - Pink Sheet, 24 Feb, 2014.)*

"At first we viewed reform as a potential threat," Melville said.

"However, as we prepared for the hearing, our view point began to evolve and we [started to see] monograph reform not as a threat but as an opportunity to work with FDA and Congress to develop a better regulatory framework that could preserve and improve the monograph for generations to come."

As Center for Drug Evaluation and Research officials and industry stakeholders alike suggested in comments and during discussions on monograph reform, CHPA says it expects the legislation will allow FDA to add to or change a monograph through administrative orders rather than requiring a rulemaking for any change. Similarly, the legislation likely will authorize FDA to establish a more efficient process for making monograph drug label changes.

The agency has made few changes to OTC monographs since its initial decisions in the early 1970s as it n establishing the platform to set conditions for drugs available nonprescription to be generally recognized as safe and effective for certain indications. Products with active ingredients or indications not within a monograph must gain pre-market approval through the NDA review process.

FDA officials as well as industry stakeholders say changes are needed before any additions to the monograph are likely. *(Also see "OTC Drug Industry Could Stand To Gain With 'Pragmatist' In White House" - Pink Sheet, 11 Nov, 2016.)*

> CHPA sees "monograph reform not as a threat but as an opportunity to work with FDA and Congress to develop a better regulatory framework that could preserve and improve the monograph for generations to come."
> – President and CEO Scott Melville

USER FEES PART OF REFORM

CDER also says no monograph progress can happen without user fees to support its work, and in 2016 the center began a separate but related initiative on looking at proposing a user fee program to support its monograph work. *(Also see "OTC Monograph User Fees Inspire Wary Support From Industry" - Pink Sheet, 13 Jun, 2016.)*

Numerous drug firms initially questioned potentially paying additional user fees, but in the second half of 2016 executives from CHPA and several OTC drug makers met regularly with CDER staff to discuss the framework for a potential user fee program and for legislation to establish the program. *(Also see "OTC Monograph User Fees: FDA-Industry Talks Move From Basics To Details" - Pink Sheet, 2 Aug, 2016.)*

According to a CDER report on a September 2016 webinar it conducted for industry stakeholders, its monograph work has included nearly 90 rulemakings, many pending simultaneous, in 26 therapeutic categories encompassing more than 100,000

OTC drug products. "Despite the scope of the responsibilities, the monograph review program is very small," the report says.

Additionally, CDER's OTC program resources "are often consumed by external mandates," including completing evaluations of sunscreen monograph ingredient proposals and publishing guidance on submitting those proposals under deadlines imposed by the Sunscreen Innovation Act or removing numerous OTC antiseptic wash ingredients under a consent decree to litigation, according to the report.

Still, CDER says, "Even without current external mandates, and even with desired monograph reforms, it would take many decades to finalize GRASE determinations for pending monographs, if resources remain at current levels."

While FDA considered monograph reform and a potential user fee program in separate initiatives with separate dockets for comments on each, CHPA expects that proposals for both will come in the same legislation.

"That is the intention, that user fees would be included in the modernization package bill," said CHPA spokesman Mike Tringale.

The industry, Tringale added in an email, is satisfied with the results of its discussions on both topics and expects a bill soon will be introduced. "CHPA feels optimistic about where everyone is regarding discussions and progress regarding OTC monograph reforms," although "there are still several things that need to fall into place," he said.

CDER's monograph work currently is funded strictly from FDA's direct appropriation, although the vast majority of OTCs are available under monographs. User fees currently touch the OTC drug space with sponsors of Rx-to-OTC switch applications subject to Prescription Drug User Fee Act costs and firms that submit abbreviated NDAs for generic equivalents of switches or other nonprescription NDA drugs subject to Generic Drug User Fee Act costs.

Tringale said CHPA is "optimistic that restoration of OTC eligibility in FSAs/HSAs is quite possible since bills in the House and Senate still remain, and they continue to find supporters and alternate vehicles for passage."

However, the value of a monograph user fee to the industry will differ from Rx drug user fee programs. Those programs were established to help FDA evaluate long waiting lists of applications and their value has been shown in the agency more quickly determining whether to approve new Rx ingredients or medical devices.

The agency has no monograph proposals waiting, though, since advising sponsors of eight long-pending time and extent applications to amend the sunscreen monograph that their information was insufficient for review in 2015. *(Also see "Sunscreen Group Remains Cloudy About FDA's Ingredient Evaluations" - Pink Sheet, 3 Nov, 2016.)*

DIRECT OTC PURCHASES WITH PRE-TAX ACCOUNTS

Melville discussed legislative prospects for including direct purchase of OTCs in pre-tax savings accounts again, speaking four days before House Speaker Paul Ryan, R-WI, cancelled a vote on American Health Care Act after Republicans in the far-right Freedom Caucus refused to support the bill because it would not entirely repeal the Affordable Care Act and more moderate GOP members balked at Medicaid program cuts the bill would make. *(Also see "Fate Of OTCs In Health Savings Accounts Rests In Capitol Hill Negotiations" - Pink Sheet, 11 Jan, 2010.)*

CHPA had tempered support for the AHCA, suggesting the legislation was not its preferred method to include OTCs once again in consumers' pre-tax saving accounts after lobbying for years to remove from the ACA the provision requiring a prescription for OTC drug purchases with pre-tax savings. *(Also see "It's Complicated: Health Care Act Simplifies Buying OTCs With Pre-Tax Accounts" - Pink Sheet, 10 Mar, 2017.)*

Restoring direct OTC purchases to FSAs, HSAs and similar accounts may now rest on the Restoring Access to Medication Act of 2017, S. 85 proposed by Sens. Pat Roberts, R-KS, and Heidi Heitkamp, D-ND, and H.R. 394 by Reps. Lynn Jenkins, R-KS, and Ron Kind, D-WI. The legislation, which has been introduced in every session of Congress since the ACA was passed in 2010, proposes to amend the act to again allow direct purchases of nonprescription drugs with pre-tax savings accounts. *(Also see "Direct OTC Purchases With Pre-Tax Accounts Swing On ACA Change, Not Repeal" - Pink Sheet, 27 Feb, 2017.)*

Tringale said CHPA is "optimistic that restoration of OTC eligibility in FSAs/HSAs is quite possible since bills in the House and Senate still remain, and they continue to find supporters and alternate vehicles for passage."

Melville suggested that restoring health care provisions allowing OTC purchases in pre-tax savings is critical, as consumer-driven health care plans continue to multiply moving forward, especially as long as the ACA is in place. Consumer-driven health care plans are programs roughly defined as requiring consumers to pay for routine healthcare expenses out-of-pocket while high-deductible insurance covers them for "catastrophic" events.

"These plans have exploded in popularity since the enactment of the Affordable Care Act," he said. "When consumers spend their money, they become smarter purchasers. In your industry, my industry, we're all about that."

Though he acknowledged during his speech the AHCA vote could go either way, Melville said he is sure changes are coming to health care in 2017. "I'm certain that some reform will pass Congress this year and will be signed by President Trump," he said.

Trump has stated he expects the ACA to fail but his administration will allow the law to "to go its way for a while, and see how things go." Although Ryan said health care legislation will not be considered again during the current session immediately after he pulled AHCA from a vote, Trump and some lawmakers are saying they will work on other legislation to repeal the ACA.

From the editors of the Tan Sheet. Published online March 30, 2017

Multi-Company Product Listing Agreements On The Rise In Canada

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Gilead Sciences Inc., **Merck & Co. Inc.**, and **Bristol-Myers Squibb Co.** have all agreed new product listing agreements for their hepatitis C drugs with the body that negotiates prices for Canada's public payers. The developments mark the pan-Canadian Pharmaceutical Alliance's first major therapeutic category negotiation, in which it talks with more than one company at a time. More multi-stakeholder talks may follow and manufacturers of drugs in other crowded therapeutic markets should start preparations for similar talks, advises Sherry O'Quinn, from MORSE Consulting. O'Quinn speculates that rheumatoid arthritis and multiple sclerosis drugs could be contenders for similar negotiations.

British Columbia and Ontario co-led the negotiations for the pCPA. They managed to secure cost savings after re-negotiating with Gilead for Harvoni (ledipasvir/sofosbuvir) and Sovaldi (sofosbuvir), which were already the subjects of recent product listing agreements. Meanwhile, BMS' Daklinza (daclatasvir) and Sunvepra (asunaprevir); Gilead's Epclusa (sofosbuvir/velpatasvir); and Merck's Zepatier (elbasvir/grazoprevir) were new to the table, says the British Colombia's health ministry. O'Quinn points out, **AbbVie Inc.**'s Holkira Pak (Viekira dasabuvir/ombitasvir/paritaprevir/ritonavir) and Technivie (ombitasvir/paritaprevir/ritonavir) were not listed as successful participants in the negotiation. "This seems to signal that the pCPA is willing to exclude manufacturers who are not willing or able to give them what they are seeking in the negotiation," she says. Meanwhile, AbbVie told the *Pink Sheet* that "the company is "extremely disappointed by this outcome since [it] negotiated in good faith and [is] ready to meet all of the pCPA's requirements to be included in the new framework."The firm added that it still hopes to be included in the framework and is actively working to that goal.

The terms of the agreements and prices are confidential, but the pCPA and British Colombia's health authorities are evidently pleased with what they have negotiated. The British Colombia health ministry says that "significant savings" were achieved. "This agreement changes the landscape for hepatitis C patients living in B.C. Not only are there four new treatment options for what is now a curable virus, but the savings that were negotiated will allow us to cover treatment options for all hepatitis C patients – rather than just those in more advanced stages of the disease," said Terry Lake, British Colombia's health minister, in a statement. British Colombia's health ministry says it is expanding its PharmaCare hepatitis C treatment program. Currently only patients with liver damage are eligible for treatment, but from 2018-19, any chronic hepatitis C patient will be covered, "regardless of the type or severity of their disease." O'Quinn believes that other provinces will follow in expanding access to the treatments.

> "The hepatitis C drug negotiations signal that the pCPA is increasingly able to take on more complex negotiations, and with a number of stakeholders at the same time"

ONCOLOGY, RA AND MS DRUG MAKERS NEXT?

The pCPA negotiates product listing agreements on behalf of Canada's public payers and its clout has grown considerably since its inception in 2010. It is much harder for companies to convince provincial and federal payers to list their drug on public plans without a product listing agreement (PLA) in place. Now it looks as though the pCPA is growing in sophistication. The pCPA has already conducted one smaller-scale multi-stake holder PLA in the diabetes space, but, according to O'Quinn, the hepatitis C drug negotiations "signal that the pCPA is increasingly able to take on more complex negotiations, and with a number of stakeholders at the same time." The pCPA is recognizing that it has more leverage to negotiate when multiple products with similar efficacy and safety profile enter the market, she notes. O'Quinn believes that companies that are active in other competitive specialty spaces with big budget impacts will likely face bigger scale therapeutic class negotiations if they want to stay listed on public drug plans. Manufacturers of rheumatoid arthritis, multiple sclerosis, and oncology treatments could fit the bill, she says.

Arvind Mani, also from MORSE Consulting, says companies must prepare as best they can, although this will not be easy. He suggests companies should keep an eye on new products coming to the market and how the pCPA treats new entrants in certain therapeutic classes, like MS or RA, to see if there are any signals of what might be in store. He suggests that clinical or therapeutic reviews by health technology appraisal body CADTH could be a precursor to such negotiations. "Preparation is going to be difficult until the pCPA comes knocking on the door," he says.

O'Quinn said that in these types of negotiations the pCPA will hold a teleconference meeting and provide manufacturers with the same information and then go on to negotiate individually with each company. Companies cannot engage in any anti-competitive behavior and would have to be very careful if they were to think about any joint strategies, she added.

From the editors of Scrip Regulatory Affairs. Published online March 24, 2017

EC To Consult On Ways To Boost Generics & Biosimilars Industry, Introduce EU-wide SPC

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The European Commission is expected to launch a consultation soon on proposed changes to the rules on supplementary protection certificates aimed at increasing the competitiveness of the EU generic and biosimilar industry while ensuring that SPCs remain a strong incentive for originator companies to carry out R&D into new drugs.

The package of proposals includes introducing a waiver that would allow EU-based generics firms to manufacture for export versions of drugs still protected by an SPC and which, according to the commission, could allow them to "seize net export opportunities of several billion Euros in the coming years."

The proposals are also intended to iron out inconsistencies in how SPCs are granted by the different EU member states and possibly establish an EU-wide SPC title to dovetail with the new EU unitary patent system, as well as to clarify the scope and application of the EU's "Bolar" research exemption.

The commission's proposals were originally outlined in its October 2015 draft strategy on upgrading the EU single market, and were supported by the European Parliament in its report on the proposals last year. *(Also see "Multi-Stakeholder Approach Helped Push SPC Waiver Up The EU Agenda, Says Medicines For Europe" - Pink Sheet, 17 Jun, 2016.)*

In June 2016, the Council of the EU, in its conclusions on strengthening the balance in the pharmaceutical systems in the EU, asked the commission to analyze the impact of the EU's pharmaceutical incentives, including the SPC and the "Bolar" exemption, on innovation and access to medicines.

The commission is now looking at how best to implement these plans, and has outlined its ideas in what it calls an "inception impact assessment" looking at the issues that have been raised and the policy options for tackling them. This document will form the basis of a public consultation that the commission says will begin in the second quarter of this year.

Sergio Napolitano, director of legal affairs and trade policy at the generics and biosimilars industry association, Medicines for Europe, believes that the three-month consultation will be launched in April, together with a draft impact assessment. Speaking to the *Pink Sheet* on the fringes of Medicines for Europe's biosimilars conference in London last week, Napolitano said the idea was to finalize the impact assessment by the end of the year, after which the commission will draft a legislative proposal to be presented to the parliament and the council.

SPC WAIVER

Medicines for Europe has been pressing for the SPC manufacturing waiver for some time. The issue was discussed again during the first session of the London conference, where Ravinder Chahil of Polish company Polfarma noted that SPCs extend effective patent protection on originator drugs in the EU by up to five years, and

"The current system often gives an unintended lead time advantage to non-EU based operators in that they can stockpile their generic products and launch them in the EU immediately upon SPC expiry.

that generics companies in the EU can't begin manufacturing their versions until the SPC expires – even if the product is intended for export to non-EU countries.

By contrast, manufacturers of generic and biosimilar medicines based in non-EU countries where there is no SPC protection, such as Canada, Brazil, Russia, India and China, can enter markets where patent protection has expired up to five years earlier than EU-based manufacturers. Moreover, the system often gives an unintended lead time advantage to non-EU based operators in that they can stockpile their generic products and launch them in the EU immediately upon SPC expiry.

For this reason, many firms decide to relocate their production outside the EU to remain competitive, and this is why they are so keen to have a waiver allowing them to manufacture within the EU for export elsewhere. The commission agrees, saying that European manufacturers may need to move their production outside the EU, either via delocalization or long-term outsourcing contracts, in order to overcome these legal hurdles and stay globally competitive. "EU reliance on foreign-manufactured medicines might be increasing, with the loss of high value jobs in the EU," it suggests.

"The manufacturing waiver is intended to be the legal mechanism for EU-based manufacturers of biosimilars or small-molecule generics to produce at the commercial scale an API [active pharmaceutical

ingredient] of a drug protected by an SPC," Chahil told the conference.

The commission believes an export waiver is a perfectly legal way of tackling the problem because it does not infringe the EU's responsibilities under the World Trade Organization's TRIPS agreement as it does not affect the 20-year patent term and it does not involve any weakening of SPC protections within the EU or any changes to the intellectual property balance, Chahil explained. Moreover, he said, it will "avoid relocation of manufacturing facilities, create jobs and support the European API industry, leading to economic growth."

Other SPC-related actions are in the commission's sights, including the effects of the fragmentation of the SPC system on originator companies. This will involve looking at how SPCs have been awarded in different countries, and increasingly the reliability – and bringing down the cost and burden – of registering and enforcing SPCs.

"There are cases where some member states have granted SPC applications, while the very same applications have been refused in other member states, or else granted but with a different scope," the commission says in its document. "Multiple national SPCs also result in high costs of registration and maintenance. Some member states' patent offices do not have adequate administrative capacity for the registration of SPCs, and grant them without checking the information provided," it declares.

The commission is also looking at how SPCs – which are awarded at national level – will fit with the new unitary patent system, and is envisaging the creation of a "unitary SPC" to be used in tandem with the unitary patent.

A European SPC title would bring a number of advantages to owners of SPCs, which tend to operate across borders in terms of R&D, licensing and commercialization, the commission observers. For example, it would reduce costs (only one fee for the whole of the EU), limit litigation to just one court across the EU (i.e., the new Unified Patent Court), and offer greater legal certainty and predictability as well as less discrepancy as to SPCs' expiry dates. "This would be of interest to all market players, and especially to SMEs operating across borders. National patent offices might lose some administrative fees related to national SPCs; this would be offset by a reduction in administrative tasks and redistribution of part of the European SPC fees."

ADDRESSING BOLAR INCONSISTENCIES

The commission is also proposing to address inconsistencies in the way that the member states apply the "Bolar" provision, which allows generics firms to conduct the necessary tests and trials to obtain product approvals during the patent protection period on the reference drug without infringing the patent.

It says, for example, that in some countries it is not clear whether Bolar applies to tests conducted by manufacturers for the purpose of seeking marketing authorizations in non-EU countries, and that therefore "European companies might be duplicating testing in the EU and in third countries."

It adds that only certain countries implemented the Bolar exemption in such a way as to allow originator pharmaceutical firms to conduct testing to meet new national regulatory requirements on pricing and reimbursement – for example against comparator drugs for health technology assessment purposes. "In the absence of such exemption, companies have to spend resources and time to identify potentially infringing patents before conducting such testing."

"The commission is also looking at how SPCs – which are awarded at national level – will fit with the new unitary patent system, and is envisaging the creation of a "unitary SPC" to be used in tandem with the unitary patent.

These differences create difficulties for manufacturers involved in international development, Ruediger Jankowsky, managing director of Spanish firm Cinfa Biotech, told the London conference. They are "obstacles to investment and to the sustainability of the biosimilars market in Europe," and the Bolar harmonization and SPC waiver are "urgently required to keep the industry competitive," he declared.

There is an additional issue in that some EU countries do not allow the supply of patented APIs to EU-based generic manufacturers for the purpose of seeking marketing authorizations under the Bolar exemption.

Napolitano said this was currently a grey area as selling APIs of patented drugs to generic companies in the EU is allowed in some countries and not others. Under the proposed changes, API manufacturers could sell to generic companies which would be able to use them without problems – "this would bring back the API industry," he said.

THE PROCEDURE FOR CHANGE

It's not yet clear exactly how the commission will go about framing its proposals. For the purposes of the forthcoming consultation, it has put forward a mix of non-legislative and legislative solutions for the waiver, the modernization of the SPC Regulation (for example amending the eligibility provisions, the scope of protection, registration procedures, and so on), and clarification of the scope of the Bolar provision.

This could be done through a stand-alone regulation that amends both the existing SPC Regulation (potentially including the introduction of a European SPC title) and the Bolar provision, for example, or a specific regulation could be implemented creating a European SPC title.

As well as the public consultation, targeted consultation activities will be organized, including a conference/workshop for broad set of stakeholder groups. Further consultations and presentations to national patent offices and relevant member state authorities are also planned.

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

India's E-Plan To Map Drug Sales – Turning Point For Better Traceability?

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India's Ministry of Health and Family Welfare has proposed establishing an electronic platform to regulate the sale of medicines in the country.

The proposed new e-structure mandates, among other things, that all manufacturers register themselves with the portal and provide data pertaining to the sale of medicines to different distributors. Data on supplies to stockists/wholesalers or otherwise with batch numbers/expiry date and the quantity supplied are required to be put onto the system.

Stockists and wholesalers, in turn, would also need to register on the portal and share details on stocks received and supplied to further distributors or retailers.

"The retailers – chemists and druggists or e-pharmacy outlets – would be required to enter all details of the medicines/drugs received, sold, returned to the manufacturer or disposed of in any other manner. No retailer/chemist/e-pharmacist outlet shall be permitted to sell any medicine/drug unless such pharmacy is registered on the e-portal" the public notice from the ministry dated Mar. 16 said. The ministry has sought stakeholder and public comments to the proposed system by Apr. 15.

An industry expert with a multinational firm told the *Pink Sheet* that the proposal calls for a "shift in operating behavior" and is expected to have its share of "teething troubles" but is generally feasible overall. The expert drew parallels with the IPDMS [Integrated Pharmaceutical Database Management System] introduced by India's apex pricing body, the National Pharmaceutical Pricing Authority, requiring mandatory registrations.

"Given the IT setup of large companies (SAP-based) it is possible to have a platform that can transfer data like quantity, billing price and batch number details. A set up like this if implemented in the true sense can add to end-to-end traceability and significantly lowers risks of pass offs

and substandard medications," the expert said. India had earlier announced a staggered plan for implementation of a track and trace system for pharmaceutical exports. *(Also see "India Reschedules Drug Export Track And Trace Plan" - Pink Sheet, 28 Jan, 2016.)*

REALISTIC AND WARRANTED?

The government's plan appears to have the general buy-in of some key stakeholders.

The Organization of Pharmaceutical Producers of India, which represents leading foreign firms, said that it welcomes the government's efforts to bring in regulations in respect of sale of drugs in India including those sold online.

"Such an initiative will complement the government's 'Digital India' focus and will undoubtedly be a step towards establishing an e-enabled robust and transparent regulatory structure wherein the supply chain has registered and licensed pharmacists," Kanchana TK, OPPI's director general told the *Pink Sheet*.

Netmeds, a leading online pharmacy in India, suggested that the government's proposal is both "realistic and warranted".

"The more cross-referencing there is between manufacturer's originating batch number data, end-user data and everything in between, including returns and recalls, the more difficult it will be to introduce counterfeits into the supply chain. While the data from the manufacture up to the chemist may be extant, there is very little supportive data being collected from that point onward. Requiring such data is a step in the right direction," Bruce Schwack, cofounder and director, communications, Netmeds, told the *Pink Sheet*.

Another industry pundit with a frontline foreign firm suggested that collecting such data was perhaps long overdue – in developed countries, such data is typically collected and retained. In markets where healthcare is reimbursed, non-availability of such information can make it "very difficult" to operate while in the case of India, however, the scale is totally different, he noted. Besides, the use of technology in India is not at optimal level.

"With 550,000–600,000 independent pharmacy wholesalers and retailers the market is extremely fragmented and it has dissuaded private companies from creating solutions to capture this valuable data. To further complicate matters, the wholesalers and retailers are unionized and quite resistant to change. They may view this as government interference and oppose the move," the industry pundit added.

DETAILS OF MEDICINES DISPENSED

The proposed e-platform also reinforces the need to ensure that certain specified medicines be dispensed only against prescription of a registered medical practitioner. Exceptions, though, may be permitted in the case of a few identified medicines, with any other person specifically authorized (such as accredited social health activists (ASHAs) – essentially community health workers instituted by the health ministry) to distribute a particular class of medicines.

The ministry notice also specifies that the details of medicines dispensed would need

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to be entered in the e-platform and bills would be generated through the system.

"Such details will include prescribing doctor's registration number (Medical Council of India or State Medical Council or the Dental Council of India) or other authorized person's identity number, the name and registration number of the dispensing chemist and the quantity supplied, etc."

Asked whether some of these requirements may be a bit onerous to begin with, given the non-uniform systems across the chain, Netmeds' Schwack said that while putting the systems in place will require some "budgeting, planning and execution" it is, however, "very achievable and well worth the effort".

"Managing a progressive nation's healthcare system requires data which is accurate and accessible to everyone," he declared.

The notice also bars export of anti-bacterial or any habit-forming drugs against "internet orders". Individuals or entity proposing to export other medicines/drugs on the basis of internet orders would need to be registered with India's Central Drugs Standard Control Organization and details of such registration would need to be mentioned in the invoice when exporting such drugs, it states.

DATA CONFIDENTIALITY AND GREY AREAS

Hospitals and other clinical establishments, both in the public and private sector, have also been covered under the proposed initiative. These establishments would need to enter details of medicines dispensed or distributed/issued/made available to patients and also details of any adverse reaction.

The notice indicates that such data would be kept confidential and made available only to the PvPI [Pharmacovigilance Program of India] and the Indian drugs regulator.

However, industry appears a bit wary on data confidentiality and end-use issues with respect to the data sought; a clause in the notice which suggests that the information collected may also be used by the Ministry of Health and Family Welfare, "for such purposes as considered necessary in public interest" appears to be of particular concern.

"The purpose appears to be grey area other than reference to pharmacovigilance (and may evolve based on stakeholder inputs," the expert with the multinational firm said.

Others said the government ought to have specified who will have access to the database and what the scope of use of such data is.

"There hasn't been much engagement with industry; some aspects fail to take into account the ground realities in the sector," Dilip Shah, secretary general of the Indian Pharmaceutical Alliance, which represents leading domestic firms, said.

The industry pundit said that it is unclear why the government needs this information and demanded clarity on key aspects.

"This is definitely a grey area. It isn't quite clear as to all the information that businesses will have to enter into the database in order to be given permission to operate, but this is pretty close to how the license raj operated a few decades ago. Much as there are fears and concerns of how tax terrorism and unnecessary govt interference can happen with the passing of the new Finance Bill and Aadhar, this move too must be made transparent and debated in public before formalizing it," the industry pundit added.

Aadhar is essentially a 12-digit individual identification number for all Indians, which is expected to serve as proof of identity and address, anywhere in the country.

REVENUE MODEL

The government proposal also sets out a revenue model so that the organization entrusted to maintain the portal and render assistance as required becomes self-sufficient. An autonomous body under the Ministry of Health and Family Welfare is expected to develop and maintain the platform.

The ministry expects to provide an initial grant and "minimum human resources" to the autonomous body and expenditure incurred on this front is to be met from the Consolidated Fund of India for an initial period of two years. The autonomous body, though, is expected to generate its own resources to meet its operational requirements thereafter.

The proposed revenue model envisages a "small transaction fee" of not more than 1% of the total cost of medicines subject to a ceiling of INR200 per prescription, to be paid online by pharmacies/ e-pharmacies/ wholesale /retail distributions. A "small" registration fee and renewal fee determined by the government "from time to time" shall also be payable by manufacturers/ pharmacies/ hospitals/ clinical establishments, the notice adds.

The expert with the multinational firm said that ideally the fee should be paid by all resellers/intermediaries as there are channel margins (8% and 16% for stockists and retailers even for price controlled medicines).

Netmeds said that it expects more discussions before a final determination is made concerning the revenue model. "However, it is a reality that the system's creation and maintenance must be paid for, but if the cost is spread out across the wide enough range of stakeholders, it should not cause undue economic stress for any of the participants," Schwack maintained.

The industry pundit, however, said that the proposed revenue model makes little sense.

"Why charge distributors per prescription? Does the government really expect this cost to be absorbed by them and not get passed on to the patient? And if the patient has to pay an additional 1% of the value of the prescription every single time that he refills it, how does it make medicines more affordable?," he asked.

The pundit argues that making the e-structure plan a "self-financed" model does not require money to be charged on every single prescription at all.

"A one-time registration fee can help the government easily recover its costs when you consider the scale of the pharma distribution chain in India. It is also hard to believe that the government hasn't considered the value of this data and a subsequent monetization plan for it. That is where the real value of this proposal lies," he added.

From the editors of PharmAsia News.
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The Politics Of *Opana:* US FDA's Opioid Problems Won't Go Away

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An advisory committee for the US FDA made a clear recommendation in favor of regulatory action to address concerns about IV abuse of Endo's *Opana ER* (oxymorphone) reformulation – but not clear advice on what the next step should be.

In part, that was by design: FDA asked the committee to vote at the end of the March 13-14 meeting of the Anesthetic & Analgesic Drug Products and Drug Safety & Risk Management Advisory Committees on whether the benefits of the formulation outweigh the risks – but framed the vote as encompassing a range of potential actions that might follow. Eighteen members of the committee voted no, with just 8 voting yes on that question.

The vote against the risk/benefit profile of the new formulation does not necessarily equate to a vote in favor of withdrawing the formulation. In fact, the number of committee members explicitly calling for withdrawal of the product (8) was the same as those who voted that the risk/benefit ratio is appropriate as is. While not all of the remaining 11 members (including one absention) made their preferred course of action known, most appeared to support some regulatory action short of withdrawal, such as a specific REMS for the new formulation. *(Also see "Opana ER Looking At REMS – Or Worse – After US FDA Panel Weighs Intravenous Abuse Risk" - Pink Sheet, 14 Mar, 2017.)*

The split vote may not provide much in terms of direct, actionable advice on next steps, but it does provide FDA with important support for a key message the agency has been trying to spread for the past decade: it is premature to declare that abuse-deterrent formulations are *the* solution to the opioid abuse epidemic.

FDA has often been accused of being too cautious in assessing ADFs, and especially in granting explicit claims and withdrawing non-ADF alternatives. Those critics include President Donald Trump, who said on the campaign trail that "the FDA has been far too slow to approve abuse-deterring drugs." He added: "These are people that are dying, that are committing suicide, and they have some things that are amazing and we are not approving them."

The agency's advisory committee has generally been very supportive of FDA's view of the limits of technology. At times, in fact, the outside panel has seemed even more cautious than FDA in weighing whether abuse-deterrence labeling can give false security that the product is less abusable or safer and therefore meet lead to *more* addiction from overprescribing, etc.

In this case, the committee was siding with FDA in declaring that the new *Opana* formulation appeared to be making things worse, not better – and rejected Endo's arguments that

The perceived shift in abuse patterns was likely a function of the challenges of adequately tracking abuse patterns; and

The side effects associated with the formulation would be expected from many other ADFs.

Making the issue still more potent is the association of *Opana* abuse with an outbreak of HIV in Indiana, which became a major public health crisis for then-Gov. Mike Pence – now the Vice President of the US. *(Also see "Opana Safety Review Will Set Tone For Opioid Regulation Under Trump" - Pink Sheet, 1 Feb, 2017.)*

Still, that 18-8 vote may end up making things more difficult for FDA moving forward.

Already, one prominent critic of the agency's handling of opioid abuse issues – Sen. Ed Markey (D-Mass.) – is declaring that the new formulation needs to be withdrawn. In a statement declaring opposition to Trump's FDA Commissioner nominee, Scott Gottlieb, Markey noted that "an FDA advisory committee ruled that the risks of Opana ER, a prescription opioid that has been linked to a 2015 HIV outbreak in Indiana, outweigh the benefits." He called for FDA "to remove the so-called 'abuse deterrent' opioid drug *Opana ER* from the market given recent concerns about the drug's safety.

Markey stopped just short of making pulling the product a condition of his support for Gottlieb's confirmation, but he came close: "Until Mr. Gottlieb commits to reforming the way the FDA approves and manages prescription opioids, I will vigorously oppose his nomination."

As a Democrat, Markey has a limited voice in the confirmation process. However, it is worth noting that his opposition to the last Democratic FDA nominee – Robert Califf – helped prompt FDA to take a fresh look at its opioid policy and (in essence) reduce the weight it formerly put on the importance of the unmet need in pain treatment. *(Also see "FDA's Opioid Policy Reboot: New Risk-Benefit Model, Real-World Data" - Pink Sheet, 4 Mar, 2016.)*

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The split vote may support an FDA message that it is premature to declare that abuse-deterrent formulations are the solution to the opioid abuse epidemic.

> FDA's is likely to remain in the hot seat for the foreseeable future, with opioid regulatory issues requiring considerable resources and management attention.

If nothing else, the meeting demonstrated yet again that finding a "solution" to the opioid abuse issues from FDA's perspective remains incredibly challenging – and the agency is thus likely to remain in the hot seat for the foreseeable future, with opioid regulatory issues requiring considerable resources and management attention.

The one certainty coming out of the meeting is that Endo's attempt to extend the *Opana ER* franchise via abuse-deterrent formulation technology is a failure. That is an important message for the many sponsors who have embraced ADFs as a "low-risk" area for drug development.

Endo made the decision to move on from *Opana ER* after its application for a formal abuse-deterrent claim was withdrawn in 2016. The March 13-14 advisory committee review, in fact, was originally planned as part of that review.

The commercial reality for Endo is an important factor in the already complicated discussion of what the next steps should be on the regulatory front. Endo has essentially abandoned the brand already – it is no longer actively promoted and the company is resigned to letting it erode and focusing its business elsewhere. That makes any steps that involve significant investment by Endo unlikely, though of course the company is presumably better off from a liability perspective if the product is never formally withdrawn.

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

FDA's NDA And BLA Approvals: Zejula, Ocrevus, Dupixent

Below are FDA's original approvals of NDAs and BLAs issued in the past week. Please see key below chart for a guide to frequently used abbreviations

SPONSOR	PRODUCT	INDICATION	CODE	APPROVAL DATE
New Drugs				
Tesaro	*Zejula* (nirapirab)	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy *(Also see "Broad Label Gives Tesaro's Niraparib A Head Start In Ovarian Cancer" - Scrip, 28 Mar, 2017.)*	P, 1	3/27/2017
New Biologics				
Genentech (Roche)	*Ocrevus* (ocrelizumab)	Treatment of adults with relapsing or primary progressive forms of multiple sclerosis *(Also see "Ocrevus Launching Quickly Even After Manufacturing Worries Delayed US Approval" - Pink Sheet, 29 Mar, 2017.)*		3/28/2017
Regeneron	*Dupixent* (dupilumab)	Treatment of adults with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable		3/28/2017

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

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
Genentech's rituximab/hyaluronidase injection for treatment of patients with: relapsed or refractory follicular lymphoma as a single agent; previously untreated follicular lymphoma in combination with first-line chemotherapy and, in patients achieving a complete or partial response to rituximab/hyaluronidase in combination with chemotherapy, as single-agent maintenance therapy; non-progressing (including stable disease) follicular lymphoma as a single agent after first-line cyclophosphamide, vincristine and prednisone chemotherapy; previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone or other anthracycline-based chemotherapy regimens; and in combination with fludarabine and cyclophosphamide for previously untreated and previously treated chronic lymphocytic leukemia	Oncologic Drugs	March 29
Safety issues associated with over-the-counter analgesic combination products used for upset stomach (i.e., heartburn, nausea, fullness, belching, gas, acid indigestion, and/or sour stomach) and hangover indications under the Internal Analgesic and Antacid monographs; discussion of the hangover indication under the Overindulgence, Internal Analgesic and Stimulant monographs	Nonprescription Drugs; Drug Safety and Risk Management	April 4
Novo Nordisk's nonacog beta pegol (recombinant human coagulation Factor IX, glycopegylated) for hemophilia B	Blood Products	April 4
Inspirion Delivery Sciences' oxycodone immediate-release for management of moderate-to-severe pain where the use of an opioid analgesic is appropriate; committees will discuss the overall risk-benefit profile and whether applicant has demonstrated abuse-deterrent properties that would support labeling	Anesthetic and Analgesic Drug Products; Drug Safety and Risk Management	April 5

Pink Sheet

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Phil Jarvis, Mike Ward

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