MANUFACTURING QUALITY
Global Efforts Intensify In Fight Against Counterfeit Drugs, p. 15

FDA
A Hiring Freeze By A Different Name: OMB Wants Agency 'Workforce Reduction' Plans, p. 7

REGULATORY UPDATE
Brazil Prepares To Make Its Own Sovaldi As Regulator Opposes Patent Application, p. 14

Pink Sheet
pink.pharmamedtechbi.com Vol. 79 / No. 16 April 17, 2017
Pharma intelligence informa

CAR T-Cells, Helping US Firms & An "Ambitious" Plan For Advanced Therapies In The EU

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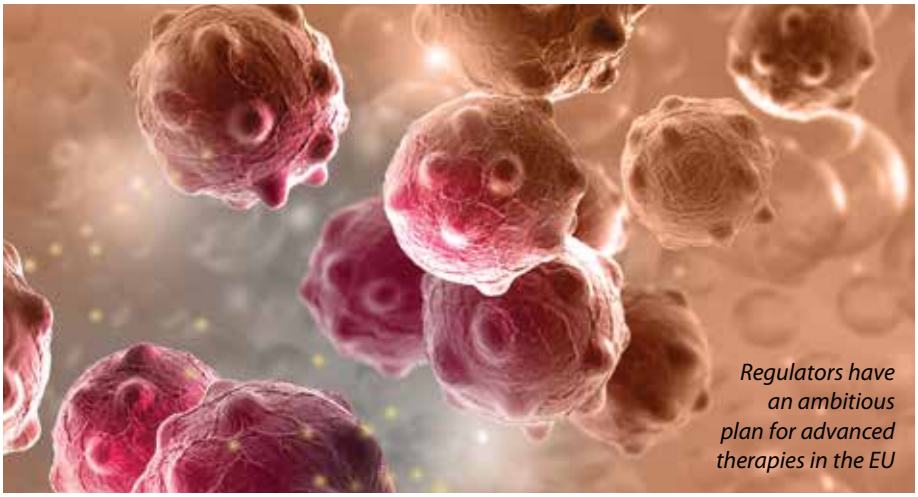

Regulators have an ambitious plan for advanced therapies in the EU

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If all goes to plan, developers of drugs based on chimeric antigen receptor (CAR) T-cell technology should soon start to get a better understanding of what will be required of them on the regulatory front in Europe.

CAR T-cells, classified in the EU as advanced therapy medicinal products (ATMPs), are showing promise in clinical trials as a new paradigm for treating cancers such as leukemia and lymphoma that have not responded to standard therapies.

These types of genetically-modified cells pose a number of scientific and regulatory challenges but, as yet, there is no EU guidance on how to develop and evaluate them. Remedying this is high up on the to-do list of Martina Schüssler-Lenz, the new chair of the European Medicines Agency's Committee for Advanced Therapies. "We have to make sure that these products get to the patient," Schüssler-Lenz told the *Pink Sheet*.

Schüssler-Lenz spoke about what she said was an "ambitious" work plan for the CAT – and ATMPs in general – under her three-year mandate as chair; she was elected chair in February this year. "An increased workload lies ahead of us," she said, and her aim is to "come up with adequate regulatory strategies to cope."

ATMPs, which are based on genes or cells, represent a fast-growing field. But they are complex products and their development has been hampered by myriad scientific, technical and manufacturing challenges. Since EU legislation (Regulation (EC) No 1394/2007) governing advanced therapies came into force in 2008, just 15 ATMP marketing authorization applications (MAAs) have been filed. Only eight products have been approved and launched, and three of these have since been withdrawn.

CONSIDERABLY MORE MAAS FORECAST

That said, forecasts indicate that the CAT will receive considerably more MAAs over the next two years, Schüssler-Lenz said, noting that her committee was currently evaluating two MAAs (the CAT drafts an opinion on each ATMP application before the EMA's Committee for Medicinal Products for Human Use (CHMP) adopts a final opinion). In addition, a study published in the *Journal of Market Access & Health Policy* in 2016 said that around 1,000 clinical trials were being conducted for ATMPs, of which 65 were in Phase III, suggesting they had a successful Phase II and a chance of reaching the market in the coming five years.

CAT members will have to keep pace with a scientific field that moves very quickly. "This means that in parallel to our

CONTINUED ON PAGE 4

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20

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Oncology Center of Excellence Open For Business: Podcast With US FDA's Richard Pazdur

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Three months after the official launch of the Oncology Center for Excellence, applications for cancer products are now being reviewed by OCE medical teams. OCE Director Richard Pazdur provides more details on the process and procedures of the newly established center in a podcast interview.

Generic Drug Puzzle: Why Did ANDA Submissions Spike Again?

https://pink.pharmamedtechbi.com/PS120405

Jump in March may have been "happenstance," but also could be concerning as US ANDA submissions reach near record pace.

CMS Solicits Ideas To Improve Part D: An Opening For Co-Pay Reform And Shaping Priorities

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The US Medicare agency signals interest in making administrative changes to the Part D drug insurance program in the coming years. That may be an opening for the pharmaceutical industry to push for new approaches to cost-sharing – but it is also an opportunity for plans to try to shape the evolution of Part D in the Trump administration.

Pharma Welcomes Clarity On Similarity Assessment Of ATMPs Under EU Orphan Law

https://pink.pharmamedtechbi.com/PS120404

As the European Commission reviews the concept of similarity within the context of EU orphan drugs legislation, it has introduced a new section on advanced therapy medicinal products to clarify how similarity assessments should be carried out for such products. While the industry has welcomed this new guidance, it urges caution on this front as R&D in this field is still evolving.

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work on procedures and marketing authorizations, we will need to adapt to the regulatory challenges that the evolving science poses and draft new guidelines or revise existing ones," Schüssler-Lenz explained.

For example, the CAT will be revising its scientific guidance document on products containing genetically-modified cells so that it factors in guidelines on the development and evaluation of medicines that contain CAR T-cells.

The committee is also revising its ATMP guideline on safety and efficacy follow-up and risk management (EMEA/149995/2008) to include information on the use of registries. A revised document has been prepared and is scheduled to be released for consultation by the summer. Health technology assessment bodies are expected to be consulted proactively during the consultation phase, and the EMA also plans to work on an ATMP-specific risk management plan template and guidance that would reduce the administrative burden for ATMP developers.

The European Commission is shortly expected to publish new guidance on good manufacturing practices for ATMPs, which was developed with input from the CAT. The document has been some time in the making and there have been concerns over the fact that it is being developed as a stand-alone document rather than as an annex to the existing EU GMP guideline (EudraLex Volume 4) for medicines in general. Regulatory authorities participating in the international Pharmaceutical Inspection Co-operation Scheme, for example, issued a statement in February warning that it diverges from PIC/S requirements and would result in lower regulatory standards.

Read the full article here

Schüssler-Lenz disagrees. She is "very much in support of the document" and says that accusations that it will reduce safety are wrong. The CAT chair said the guidance is a very good example of a collaborative effort that was developed in response to requests from stakeholders who wanted a document that outlined the GMP requirements, was readable, did not require people having "to look in five different annexes," and addressed the flexibility needed for ATMPs and the risk-based approach required.

"We have to make sure that our regulatory frame does not inhibit the timely access to these new types of treatments."

Martina Schüssler-Lenz, the new chair of the European Medicines Agency's Committee for Advanced Therapies

Other activities on the CAT's agenda include dealing with applications from sponsors for early regulatory support under the EMA's priority medicines (PRIME) scheme: over half of the 19 products that have been granted PRIME designation so far are ATMPS, including CAR T therapies. In addition, forecasts suggest the CAT will receive more than 50 requests for a scientific recommendation on ATMP classification in 2017. The committee will also be dealing with scientific advice procedures and certifying quality and non-clinical data for SMEs. A CAT work plan for 2017 is expected to be published in the second quarter of this year.

GEARING UP FOR CAR T-CELLS

Schüssler-Lenz, a physician by training, is the deputy head of the Advanced Therapy Medicinal Products Section at the Paul-Ehrlich Institute in Germany, and had been vice-chair of the CAT since March 2014. She used CAR T-cell therapies as an example to illustrate the challenges her team deals with when it comes to ATMPs.

CAR T-cell therapies are under investigation for different types of cancer by several companies including Novartis, Kite Pharma, Juno Therapeutics, bluebird bio/Celgene, Cellectis/Servier/Pfizer, Bellicum Pharmaceuticals and Celyad (formerly Cardio3 BioSciences). They involve taking T-cells from a patient's blood and then genetically engineering them in the laboratory to allow them to recognize cancer cells through specific receptor proteins. After the modified cells are returned to the patient, they can identify cancer cells and destroy them.

"As a physician, I worked in the clinic with terminally ill leukemia patients where, after several lines of treatment, there was nothing else to offer," Schüssler-Lenz said. "Now with the CAR T-cells coming, we are seeing in clinical trials that they might offer a new treatment modality."

But while CAR T-cells are demonstrating efficacy, there are concerns over their toxicity. "So these are quite challenging products for which we have no guidelines available yet," Schüssler-Lenz said.

"We have to make sure that our regulatory frame is suitable to deal with new developments and with evolving new treatment modalities," the CAT chair stressed. Just as important, "we have to make sure that our regulatory frame does not inhibit the timely access to these new types of treatments."

As well as working on scientific guidance for CAR T-cells, the committee will continue to take on board conclusions from a workshop it hosted last November that explored how to facilitate development of cancer treatments based on genetically-modified T-cells.

Work on the CAR T-cell guidance is all the more pressing, given that companies expect soon to start filing EU marketing applications for such therapies. For example, Novartis, which appears to be on track to getting the first CAR T therapy to market in the US after revealing on March 29 that the Food and Drug Administration

had accepted its MAA filing for CTL019 (tisagenlecleucel-T), plans to submit an MAA for the product to the EMA later this year.

SUPPORTING DEVELOPERS

Schüssler-Lenz also wants to make sure that ATMP developers who might be unfamiliar with EU drug requirements, such as those from academia or the US, get the support they need to navigate Europe's regulatory procedures.

"We have to see, for example, that we guide US-based developers of CAR T-cells through our European system, which is more complex than that in the US both procedure- and diversity-wise." For instance, it might not be clear to some sponsors that clinical trial applications must be submitted to national competent authorities, while marketing applications are submitted to the EMA. Also, sponsors might need help in understanding how to go about the business of setting up manufacturing for these cells in Europe.

To some extent, the CAT is already offering drug makers more help via the PRIME scheme, under which the EMA provides early and proactive support to developers of medicines that target an unmet medical need so that they might reach patients faster.

"I think it's an important task of the CAT, and of course in cooperation with the rest of the EMA, national agencies and the European Commission, that we help people work with our system," Schüssler-Lenz said.

There is also a need to ensure that hospitals and physicians understand how to use CAR T-cells and other ATMPs properly by, for example, requiring that companies establish appropriate post-authorization measures and risk management plans.

"So taking care of these products – the science and the adaptation of the regulatory system to make them available to patients – is something that I am dedicated to working on."

FOCUSING ON CLINICAL DATA

The CAT's focus has traditionally been on quality, non-clinical and clinical issues. As part of her strategy for the next three years, Schüssler-Lenz plans to have an even stronger focus on bringing products to patients by looking at efficacy, safety and benefit-risk from a clinical perspective. This does not mean neglecting quality or non-clinical issues, according to the CAT chair.

"I am really excited to focus on what the disease is and which clinical data we will need to achieve a positive benefit-risk assessment," Schüssler-Lenz said. This is "very important," and sometimes challenging in the area of ATMPs. For instance, where an orthopedic surgeon might be randomizing patients in a trial to treatment with either a cartilage-repairing, tissue-engineered chondrocyte-containing product or to a traditional surgical procedure, "we need adequate clinical expertise to judge the clinical data, to reach a conclusion on efficacy and safety and how to deal with, for example, remaining quality issues."

Schüssler-Lenz wants to make sure she has the right expertise on her team. She is satisfied with the multidisciplinary composition of the CAT, but knows there is room for improvement. "We need good clinical expertise and good expertise in trial methodology," the CAT chair said, adding that she has had "very fruitful" discussions with Europe's Heads of Medicines Agencies network about support on this front. Schüssler-Lenz is also planning to streamline discussions in committee meetings and foster closer interaction with the EMA's other scientific committees and working parties.

Schüssler-Lenz replaced Paula-Anneli Salmikangas, who chaired the CAT between February 2014 and February 2017.

From the editors of Scrip Regulatory Affairs. Published online April 10, 2017

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Brexit: Scenario Planning Well Under Way At EMA

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In the nine months since the UK voted to leave the EU, the European Medicines Agency has been working out how best to deal with two key issues: whether, and how, the UK regulator, the MHRA, might continue to work with or within the EU drug regulatory system, and the challenges posed by the EMA's forced relocation to one of the remaining 27 EU member states.

The EMA's planning has been underpinned by the establishment of an Operational Relocation Preparedness (ORP) task force at the EMA, according to Melanie Carr, head of the EMA's stakeholders and communication division and a member of the task force.

"We have been working very hard to look at the plans, and in the next two years we will be putting those plans into action, working with the network and experts," she told the recent DIA EuroMeeting in Glasgow, UK.

Speaking at the session on Brexit and EU drug regulation on March 29, Carr said: "In the longer term it is about consolidating to prepare for a new approach in the regulatory network and making sure we find the best and most effective way of working with the UK, whatever the outcome of the [Brexit] negotiations".

Without a crystal ball, Carr said, preparedness is very difficult. The EMA has been planning various scenarios based on four main workstreams: relocation preparedness, operational and financial preparedness, human resource matters, and communications, and "we are working very hard on an impact assessment," she said.

There has been much speculation over how to ensure that the UK's departure from the EU does not lead to differences in the way that new drugs are evaluated, approved and monitored, with suggestions that some kind of regulatory cooperation agreement between the UK and the EU should be implemented in order to keep the rules aligned over time.

A good deal of attention has been focused on the nature of the relationship between the EMA and the MHRA when the EMA relocates, and how to compensate for the loss of UK expertise. The MHRA punches above its weight in terms of work done for the EMA and the EU regulatory network overall, and was recently described by one former senior regulator as the "backbone" of the network.

> "If we reach a point where... we're not able to compensate [for staff losses] by recruiting in a certain time, we would move to a business continuity situation." – Melanie Carr

(Also see "EU National Agencies Prepare For 'Rebalancing' Of Network Post Brexit" - Pink Sheet, 4 Apr, 2017.)

STAFF RETENTION AND BUSINESS CONTINUITY

A key question is staff retention. Carr noted that EMA executive director Guido Rasi – for whom she stood in at the last moment at the session – had spoken in various fora about the importance of maintaining staff levels in the run-up to and during the relocation. The EMA has said it could lose as much as half of its almost 900-strong workforce.

"If we reach a point where… we're not able to compensate [for staff losses] by recruiting in a certain time, we would move to a business continuity situation," Carr said in response to a question from the Pink Sheet during the Q &A part of the session. "Hopefully it won't come to that," she added.

Clearly the location of the agency will play a significant role in determining how many staff decide to follow it to its new home. The EMA is among those who would like an early decision on the location but "when that will be I don't know", Carr said. The process is likely to be politically difficult given, among other things, the number of member states that have expressed in interest in hosting the agency. *(Also see "Politics Could Get In Way Of Quick Decision On New EMA Home" - Pink Sheet, 6 Apr, 2017.)*

KEEPING THE NETWORK GOING

Equally important, Carr noted, is the role that the EMA plays in the functioning of the EU regulatory network and the importance of keeping it all running during and after the move. The EMA "brings together experts from across the EU, almost like an assembly line, you get people doing the right job at the right time… and it is important that the negotiators don't lose sight of that going forward."

There were a number of factors that would determine how successfully the transition was negotiated, Carr said: working collaboratively, engaging with stakeholders and committees, building up capacity, and looking at how the network will take on the extra work that would have been done by the MHRA.

There is also the question of the status of existing EU drug ap-

Shutterstock: Gordon Bell

provals in the UK, and of assessments that are currently under way at the EMA. The agency is mapping out what Brexit will mean in terms of product numbers and product types, and Carr suggested that there would be opportunities for redistributing work –ongoing rapporteurships, for example – by therapeutic area or product type. Carr said the experience with the multinational assessment team (MNAT) approach could come in useful here. *(Also see "EMA's Multinational Approach Brings All But Two Member States Into New Drug Assessor Fold" - Pink Sheet, 7 Feb, 2017.)*

If necessary it would be feasible to reallocate rapporteurships in the two-year Brexit negotiation period, Carr suggested. "We have been mapping those products, thinking about the most sensible way of doing that, and we will be coming up with a communication on that as and when, so that the work will transition to the new rapporteur."

Carr said it was also important to remember that improvements could be made too. "Can we do things more simply, more efficiently? There is room for improvement, I recognize that. There are also opportunities to strengthen international collaboration, and to keep the dialogue going."

DIA AUDIENCE WANTS CLOSE TIES

Two audience polls taken at the packed Brexit session showed most people wanted the MHRA to retain close ties to the EMA, and that the majority were expecting some adverse effects on regulation:

"*Should the MHRA remain closely linked to the EU regulatory network?*" Yes = 92%, No = 8%.

"*Will Brexit disrupt the operation of the regulatory and pharmacovigilance processes?*" Yes = 72%, No = 14%, Undecided = 14%.

The high figure in support of continued alignment between the MHRA and the network is to be expected, but it would be interesting to hear what kind of alternative arrangement the 8% that voted no in this poll would want.

And the fact that 14% of the audience believes there will be no disruption to the regulatory processes as a result of the upheaval caused by the EMA's relocation and the subsequent reshuffling of regulatory responsibilities suggests that at least some interested parties are confident that things might not turn out as bad as many fear.

From the editors of Scrip Regulatory Affairs. Published online April 7, 2017

FDA

A Hiring Freeze By A Different Name: OMB Wants Agency 'Workforce Reduction' Plans

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FDA's current restructuring initiatives may give it a head-start in developing a long-term workforce reduction plan that it and other agencies must complete in the coming months.

In return for lifting the federal hiring freeze that has been in place since President Trump took office in January, federal agencies now have to "begin taking immediate actions to achieve near-term workforce reductions and cost savings," and develop a plan that cuts staff over fiscal years 2018 through 2022.

An Office of Management and Budget memo details the planning that will be required. Agencies must provide OMB with a progress report on their workforce reduction actions by June 30.

"Agencies should begin planning for these reductions now, as achieving associated personnel reductions takes time to implement and realize savings," OMB Director Mick Mulvaney wrote in the April 12 memo.

> OMB said agencies can begin considering whether to eliminate vacant positions immediately.

Ultimate authority to approve the reduction plans at FDA will reside with its head, either Acting FDA Commissioner Stephen Ostroff or, if Senate confirmation comes in time, Commissioner- nominee Scott Gottlieb.

While OMB is just now marking the freeze's official end, at FDA it has been thawing for several weeks. Agency officials already had indicated that they had received permission to hire employees related to mandates in user fee and 21st Century Cures legislation. *(Also see "The Freeze Thaws: US FDA Allowed To Hire Staff For Cures, User Fee Activity" - Pink Sheet, 22 Mar, 2017.)*

Some personnel also were exempted from the freeze, including the US Public Health Service Commissioned Corps at FDA. *(Also see "US FDA May Find Relief From Trump's Hiring Freeze" - Pink Sheet, 1 Feb, 2017.)*

While agency officials may not have anticipated the latest OMB directive, FDA in some ways also has been remaking its staff in a way that could help it deal with its smaller size.

The Office of New Drugs is undergoing a restructuring led by Center for Drug Evaluation and Research Director Janet Woodcock, who took over as OND Director upon the retirement of John Jenkins. Woodcock wants to make NDA reviews more uniform and is considering shifting resources between divisions to better deal with changing workloads. *(Also see "CDER Director Woodcock Plans Changes To Drug Reviews During OND Transition" - Pink Sheet, 6 Mar, 2017.)*

The Office of Regulatory Affairs also is preparing to launch its realigned structure, where inspectors are more specialized based on product and located at strategic

areas around the country. *(Also see "FDA's New Commodity-Based Inspection Approach To Take Effect In May" - Pink Sheet, 1 Feb, 2017.)*

Both are examples of efforts to increase efficiency and, potentially, deal with FDA's recruiting struggles. They also could factor into long-term plans to reduce the workforce.

The agency has hundreds of vacant positions both in the rank-and-file and executive levels and historically has had trouble filling them. Recruitment became a big enough problem that the upcoming reauthorization of the prescription drug user fee program directs fee revenue toward recruitment help. *(Also see "FDA's Breakthrough Workload Will Be Eased By Hiring Reviewers With PDUFA VI Funds" - Pink Sheet, 20 Jul, 2016.)*

BUY-OUTS, EARLY RETIREMENT ONE OPTION

OMB wants agencies to consider a number of options in their quests to reduce their workforce rolls, including evaluating whether vacant positions should be filled in the future.

FDA in particular may have to look hard at whether to eliminate any unnecessary vacancies, which OMB said "can begin immediately." Agencies also should consider whether the duties of a vacant position reflect current mission needs or whether the job can be reassigned to "lower organizational levels and replacement, if needed, at a lower grade."

OMB said offering early retirement or buy-outs to reduce employee counts may be possible. Templates for Voluntary Early Retirement Authority and Voluntary Separation Incentive Payments will be streamlined and most reviews of the requests expedited, according to the memo.

As part of the long-term workforce reduction plan, OMB advised agencies to re-compute their baseline full-time equivalent needs, as well as review organizational designs to ensure they are effective and efficient.

"In particular, agencies should address deputy positions, lower level chief of staff positions, special projects, and management analysts that may duplicate the work performed in such areas as procurement, human resources and senior management," according to the memo.

The memo also calls for agencies to review whether employees on administrative leave for performance deficiency or misconduct should return to work in some capacity or be removed.

> Agencies should consider whether the duties of a vacant position reflect current mission needs or whether the job can be reassigned to "lower organizational levels and replacement, if needed, at a lower grade." – OMB

FDA included 16,635 FTEs in its FY 2017 budget request, an increase of 430 from the previous fiscal year, but most were not for the Human Drugs program. *(Also see "FDA Budget Request Is Flat For Drugs, Pressuring Stakeholders" - Pink Sheet, 15 Feb, 2016.)*

JOB DUTY CHANGES ALSO POSSIBLE

FDA also may consider assigning work traditionally done by senior personnel to more junior staff.

"There are situations where it may be more efficient to restructure duties to enable additional lower-graded employees to do lower-level work previously assigned to higher-graded positions, and consolidate the higher graded work into fewer positions," according to the OMB memo.

Advancing technology also could render some positions no longer needed, OMB said in the memo.

"Agencies should build in flexibility to adapt to ongoing technological advances while offering separation incentives as needed to create openings," OMB said in the memo, highlighting that database administration, invoice processing, human resources transactional services, financial management and management analysts were positions rapidly changing or that could be shared between agencies.

Despite the desire to cut employees, OMB said in the memo that hiring and retention practices also should be streamlined.

As part of plans to maximize employee performance, agencies will be required to determine whether current practice is a barrier to hiring and retaining staff and removing poor performers.

It is likely that all the planning will not help agency morale, especially when concerns about potential agency changes increased following Trump's election. Woodcock then had to urge colleagues to focus on their mission. *(Also see "Woodcock Tries To Calm US FDA Staff Fears About Trump" - Pink Sheet, 21 Dec, 2016.)*

Published online April 12, 2017

PhRMA And Trump: 'Go Boldly,' Or Tread Carefully?

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As the House of Representatives began the process of marking up the American Health Care Act – better known as the Obamacare "Repeal and Replace" Bill – here is what some key constituencies had to say:

- "While we agree that there are problems with the ACA that must be addressed, we cannot support the AHCA as drafted because of the expected decline in health insurance coverage and the potential harm it would cause to vulnerable patient populations." *The American Medical Association*
- "We look forward to continuing to work with the Congress and the Administration on ACA reform, but we cannot support The American Health Care Act in its current form." *The American Hospital Association*
- "The American Health Care Act threatens health care affordability, access, and delivery for individuals across the nation. In its current form, the bill changes Medicaid to a per capita cap funding model, eliminates the Prevention and Public Health Fund, restricts millions of women from access to critical health services, and repeals income-based subsidies that millions of people rely on. These changes in no way will improve care for the American people." *The American Nurses Association*
- "We write today to express our opposition to the American Health Care Act. This bill would weaken Medicare's fiscal sustainability, dramatically increase health care costs for Americans aged 50-64, and put at risk the health care of millions of children and adults with disabilities, and poor seniors who depend on the Medicaid program for long-term services and supports and other benefits." *AARP*

Not everyone in the health care sector was so negative. The insurer association AHIP issued a statement praising elements of the bill that were added as the process moved forward, and pledging "to continue to work with the House, Senate, and the Administration to make sure affordable coverage options are available for all consumers, especially those with low incomes or who rely on Medicaid."

With its comments, AHIP didn't exactly declare support or opposition. But it did say something.

In contrast to the pharmaceutical industry. None of the major trade associations had anything public to say about the pending legislation. And, given the pivotal role that the brand name association PhRMA played in the "deal" that helped move the Affordable Care Act through Congress in 2010, that group's silence was deafening.

But it also appears to be a pattern when it comes to dealing with the priorities of the Trump Administration.

NEW REALITY BEGETS NEW STRATEGY

PhRMA came into 2017 prepared to make a lot of noise – expecting (weren't we all?) a Hillary Clinton Administration that would be certain to make drug pricing a top priority issue, potentially with a Democratic-controlled Senate on her side. The industry built a large war chest for the fight ahead, only to face a distinctly different set of circumstances with the victory of Donald Trump.

> While Read carefully stressed his concern for patients, his gruff assertion that Pfizer's stake in the ACA debate is trivial to the company probably is one message the industry is wise not to convey more broadly.

No one thought the election ended the industry's problems, of course, and PhRMA's first big step in the new year was an image campaign, highlighting the promises and pitfalls of cutting edge R&D with the memorable tag-line "Go Boldly."

But it also was followed quickly by the launch of the "Go Quietly" strategy when it comes to dealing with the White House and especially with the President. PhRMA went to the White House to meet with Trump – and a group of industry CEOs smiled awkwardly while the President noted that drug prices are "astronomical" before pronouncing themselves generally happy with the closed-door session that followed.

That meeting hasn't stopped Trump from criticizing drug prices. But PhRMA has bit its tongue, not making any comment when the President goes after the industry, whether gently (like during his inaugural address to Congress, when he called for action "to bring down the artificially high price of drugs and bring them down immediately") or more outrageously (as when he declared before a meeting with the Congressional Black Caucus that he wants the US to "have the lowest prices anywhere in the world"). *(Also see "Who Speaks For The White House On Drug Prices? Industry Better Hope It Is Not Donald Trump" - Pink Sheet, 14 Mar, 2017.)*

You can bet PhRMA wouldn't have let those comments pass without rebuttal if they were made by a President Clinton. The trade association rebutted candidate Clinton's proposals on drug pricing during the campaign and routinely responded to former President Obama's proposals related to drug pricing.

But it is easy to see why staying quiet in the context of a Trump Presidency makes sense. The dynamics are – to put it mildly – unsettled. It is hard to see an upside from engaging in a war of words with this particular President.

ONE PHRMA MEMBER GOES QUICKLY

And, to be fair to PhRMA, it has shown some behind-the-scenes activity. The trade association exerted some muscle in the context of the aborted launch of Marathon's *Emflaza*, putting out a statement disavowing the proposed price and announcing a review of membership criteria. Marathon ultimately divested the product rather than proceed with the launch.

PhRMA's membership review is ongoing; the trade association says it will be finished in May. However, it appears to have had some other impacts already: Mallinckrodt Pharmaceuticals – which sells the "re-priced" brand *Acthar* – has left the association, just two years after it joined PhRMA at the start of 2015.

Mallinckrodt said in an email April 5 that it "routinely evaluates its engagement in trade associations and policy organizations and has concluded that the significant financial and time commitment required as a full PhRMA member outweighs its direct policy value to us at this time, given our present size and staff footprint." In addition, the company said it will "continue to subscribe to the PhRMA Code of Conduct, support many of the group's positions and initiatives and look forward to continuing our positive working relationship with PhRMA and its members."

Still, the change appears to have been abrupt: Mallinckrodt's corporate blog includes a March 30 post citing the company's role as part of PhRMA's "Go Boldly" campaign. That certainly gives Mallinckrodt's decision an air of "You can't fire me. I quit."

MIXED FEELINGS ABOUT ACA DON'T MAKE FOR STRONG MESSAGING

The unusual political dynamics in the ACA repeal and replace debate help explain PhRMA's studied silence on that topic as well – along with the decidedly mixed feelings within the trade association about the wisdom of having cut the ACA deal in the first place.

Consider how Pfizer CEO Ian Read discussed the potential repeal when he addressed the National Press Club on March 23, the seventh anniversary of the passage of the ACA and the day when the House had scheduled its vote on the AHCA. That vote never happened, but the fate of the bill was very uncertain when Read spoke. *(Also see "US Healthcare Bill's Failure Could Have Unpleasant Ripple Effects For Pharma" - Pink Sheet, 26 Mar, 2017.)*

Read outlined Pfizer's principles for improving the health care system in his prepared remarks, but carefully avoided any explicit statement about the pending bill. Inevitably, though, that was the first question he received – with a particular focus on the discussions to try to repeal the Essential Health Benefit provisions as part of the legislation.

He declined to make any predictions, noting that "I'm not a politician, I'm a businessman who's trying to get important cures for patients." However, as he described the type of system Pfizer supports, he seemed to echo the themes that House Speaker Paul Ryan, R-Wisc., emphasized for the AHCA – including what seemed like veiled support for repealing the individual mandate and for opening up parameters like age-rating that would make insurance cheaper for some groups.

Pfizer CEO Ian Read

> "We do support any system that ensures patients get access."

"We do support any system that ensures patients get access," Read said, "that their incentives are in the right place, that there's choice in the system, and that people get the ability to choose the insurance they need for the particular time they are in their life. And we do believe all people should choose to have insurance."

Perhaps surprisingly, Read also seemed to indicate no particular discomfort with the idea of repealing the Essential Health Benefits. "My preference is less regulation and more market-based incentives is the right way to answer that issue," he said. "You do need a safety net. So I believe the law should have an appropriate safety net for people who cannot afford insurance and who have preexisting conditions."

In his prepared remarks, Read had seemingly made the opposite case, noting that before the Affordable Care Act, insurers had often refused to cover smoking cessation therapies like *Chantix*. "Why not? They don't want smokers on their insurance rolls; they're a bad risk," Read said. That changed with the ACA.

Told that the breaking news was that there is still no deal on the repeal bill, Read was pushed for comment on the impact. "I don't believe there's any short-term impact for the industry," he said. "I think there's a tremendous impact for patients, short term."

Read then echoed the GOP position that the Affordable Care Act "is collapsing," and highlighted the perceived flaws of the law, including the "$6,000 deductible before you get to any reimbursement." The reality is, he said, "that no one's using our medicines in the exchanges, because the exchanges don't provide them access."

Read noted an analysis done by the company ahead of the *King v. Burwell* decision that could have struck down the federal insurance exchanges. At the time, he said, Pfizer decided that if the ruling went that way, it would simply provide its medicines for free to customers who were on the exchanges. "Cost to Pfizer? $40 million a year," Read said. "In a $52 billion corporation, that's nothing." *(Also see "Pfizer On Obamacare Rewind: No Short-Term Impact On Industry" - Pink Sheet, 23 Mar, 2017.)*

While Read carefully stressed his concern for patients, his gruff assertion that Pfizer's stake in the ACA debate is trivial to the company probably is one message the industry is wise not to convey more broadly.

DUCKING OTHER FIGHTS

It is not even three months into the Trump Administration, so it is far too early to judge who (if anyone) has been following an effective strategy in the new terrain of Washington, DC.

Photo credit: Courtesy of Noel St. John/National Press Club

But it isn't too early to start a list of topics that PhRMA has kept quiet on:

- It started with no comment on the Trump Administration's "travel ban" order, which prompted organized objections from a number of other industry sectors. *(Also see "Immigration Ban: BioPharma Response Varies From Silence To Dissent" - Pink Sheet, 30 Jan, 2017.)*
- It has continued through various Presidential threats to drug pricing.
- And the potential overhaul of the US health care system.
- And it also includes proposed budget cuts to FDA and the National Institutes of Health. When the President proposed deep cuts to NIH and a doubling of industry user fees for FDA, PhRMA issued a generic statement supporting the user fee program – but no defense of the federal funding for research that consumed two years of legislative effort to produce the "21st Century Cures" Act. *(Also see "Trump's Budget Outline Threatens User Fee Agreements" - Pink Sheet, 16 Mar, 2017.)*

They say that discretion is the better part of valor, and PhRMA may be proven very smart for staying out of a public war of words with the new White House. But it also begs the question: what is the difference between going boldly and running scared?

From the editors of the RPM Report. Published online April 7, 2017

India's Pricing Tussle Escalates After Regulator Names "Overcharging" Firms

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Escalating tensions between India's apex pricing body, the National Pharmaceutical Pricing Authority (NPPA), and the pharmaceutical industry, do not augur well for the sector as a whole and patients in general; a widening trust deficit and legal challenges are a drain on both sides. And shortages and non-availability of medicines are a reality that patients grapple with in India, though the reasons are clearly complex and at times go beyond just pricing issues.

The sparring between the two sides has been rather public. The NPPA has been very vocal about its actions to rein in industry – NPPA chair Bhupendra Singh is active on Twitter and the regulator's recent action that capped prices of cardiac stents in India was endorsed by no less than India's prime minister Narendra Modi. *(Also see "India's Stent Price Slash Creating Climate Of Fear, Foreign Device-Makers Say" - Medtech Insight, 15 Mar, 2017.)*

Industry, on its part, has not minced words in suggesting that the NPPA has often exceeded its remit and emphasizes that the regulator needs to ensure a balance between "availability and price". When this balance is lost, then the question of availability could surface, industry says.

Read the full article here

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An industry expert with a foreign firm told the *Pink Sheet* that the NPPA has started pitching itself as a "Price Rationalizing Body" and someone who is responsible for increasing access and affordability to healthcare in the country. *(Also see "Regulators And Pharma Lock Horns On Pricing In India" - Scrip, 1 Sep, 2016.)*

"Multiple times on social media it has threatened to take action against insurance companies, hospitals etc. It has even tweeted on the patent environment in the country. It is not just a turf war but they are also exceeding their objectives as a regulator and clearly overstepping into domains which are being currently taken care [of] by India's department of pharmaceuticals (DoP), the ministry of health and family welfare and the department of industrial policy and promotion (DIPP)," the expert claimed.

SUSPICIOUS CASES

The latest NPPA salvo came on April 7, when it put out a list of "suspected cases" of non-compliance of the notified ceiling prices covering 613 such cases – sev-

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eral top firms including **Sun Pharmaceutical Industries Ltd.**, **Dr. Reddy's Laboratories Ltd.**, **Cipla Ltd.**, **GlaxoSmithKline Pharmaceuticals Ltd.**, Abbott Healthcare Pvt Ltd and Sanofi India Ltd feature on the list. The alleged overcharging ranged from less than a rupee in some cases and shockingly, to over a few thousand rupees in others, as per details in the notice.

Abbott, whose products like *AmBisome* (amphotericin B) 50mg injection feature on the list, told the *Pink Sheet* that it follows all regulations and charges the "correct price" for its medicines.

"This situation could be a misunderstanding, not an overcharging issue. For example, when a price is reduced on a product, NPPA does not require manufacturers to relabel the product. We follow NPPA guidelines by communicating the price change separately to stockists and chemists, who are then expected to sell our medicines to patients at the reduced price," Abbott said.

Abbott added that while it may appear that the price on the label is higher, the medicine "may actually have been sold at the correct price".

GSK, whose hepatitis B injection 10ml features on the list, told the *Pink Sheet* that there appears to be "an error" and that the company had written to the NPPA clarifying its position.

"We have responded to NPPA that we are marketing our products in conformity and compliance with the provisions of the Drug Prices Control Order (DPCO) 2013," GSK said. Detailed responses from some of the other firms accused of flouting pricing norms in the latest list could not immediately be obtained.

The NPPA notice said market data of prices of products "of January 2017" were analyzed and the list was drawn up. It also noted that since the number of cases every month is "high", the NPPA is "not in a position to issue individual preliminary notice" in all cases. In February 2017, the NPPA had put out a similar list for 634 products based on December 2016 data.

The regulator said that companies which find that the data is "not correct" may submit documents in support of compliance and get their names cleared from the list. Recent Indian government data suggests that there have been about 120 cases of overcharging in 2016-17 (as of the end of February 2017) and the amount deposited by companies during the period was INR2.94bn.

DATA GLITCHES?

Early indications from sections of industry, however, suggest that some of the data of the pricing regulator may not be accurate. The Indian Pharmaceutical Alliance, which represents leading domestic firms, told the *Pink Sheet* that it had asked its members to confirm the veracity of "suspected overcharging" and had received data for about 144 of such cases from around eight firms.

"[For] all of them, the data compiled by the NPPA is shoddy," Dilip Shah, secretary general of the IPA told the *Pink Sheet*.

Shah referred to cases where products that do not belong to a firm have been attributed to the company, comparison of a product of wrong strength with the price, among other such errors in the compilation.

The least that industry expects from the regulator is accuracy of its data before going public to tarnish the image of companies, Shah added.

> "This situation could be a misunderstanding, not an overcharging issue. For example, when a price is reduced on a product, NPPA does not require manufacturers to relabel the product."
> – Abbott

'GUILTY TILL PROVEN INNOCENT'

While the NPPA's latest move is clearly aimed at taking those flouting norms to task, what has perhaps irked industry is its "guilty till proven innocent" approach.

The expert with the foreign firm lamented that the NPPA appears to disregard the principle of "innocent till proven guilty" enshrined in the Indian Constitution even for cases which broadly qualify as economic offences at best.

"Issuing notices for 634 drugs in Feb 2017, NPPA has named and shamed top pharma manufacturers of India on mere suspicion of these companies selling their drugs possibly above the notified ceiling prices. Key to note here is that mere suspicion is the cause of these notices which have been served through public domain sources," the expert said.

The expert maintained that the NPPA needs to understand that India is seen as the pharmacy to the world and acting on mere suspicion not only destroys this brand in India but also raises a question mark on the ethical behavior of companies in the minds of global buyers and that is "not a good direction to go".

"Logically NPPA should have done the investigation at their end first, or send individual notices to each company to explain, in case they had a suspicion rather than going public to name and shame big brands on mere suspicion," the expert added.

Dr. Ajit Dangi, president and CEO of Danssen Consulting, said that the NPPA's "guilty till proven innocent" approach had also led to medicine shortages and proliferation of low quality and spurious drugs as manufacturers are either exiting some therapeutic areas or even lowering the quality as it is becoming increasingly non-remunerative to remain in business.

"Insufficient margins result in non-availability of funds for R&D, upgrading the manufacturing facilities to meet international GMP standards and also for business development," Dangi, a former

president and executive director of Johnson &Johnson India, told the *Pink Sheet*.

UNBRIDLED TURF WAR

Industry seems to be in no mood to take things lying down, at least for now. Some of its angst was perhaps reflected in a sharply worded note to the Niti Aayog ((National Institution for Transforming India), the premier policy 'think tank' of the Government of India that provides both directional and policy inputs.

The IPA, in the note to Dr. Arvind Panagariya, vice chair of the Niti Aayog, said that the last few years had become a "nightmare" not because India's pricing policy is defective, but because of its "imaginative and arbitrary" implementation and the "unbridled turf war" between India's department of pharmaceuticals and the NPPA.

"This has resulted in unwarranted price fixation, open defiance of the government's corrective orders by the regulator, and frustrating litigation for the industry. It has reached a stage where the industry wonders if the country has a rule of law," the IPA said in the note dated Feb. 28 to Panagariya.

Significantly, the IPA note claims that in the "last one year", over 400 multinational and Indian companies have moved courts to resolve grievances relating to price change implementation, haphazard banning of fixed dose combinations (FDCs), non-compliance with law in price fixation, etc. This, the industry body said, isn't a "good sign" and reflects a "trust deficit" in the regulatory mechanism and administrative machinery.

"There is urgent need to initiate a meaningful dialogue between the government and industry to find amicable solutions and move forward," the IPA said. "A volatile domestic market cannot sustain exports."

PROCESS RE-ENGINEERING IN NPPA

Interestingly, amid the goings-on, India's ministry of chemicals and fertilizers, under which the NPPA falls, has constituted a new committee to further improve the "availability, affordability and accessibility of drugs for domestic patients". The six-member committee includes joint secretaries from the department of pharmaceuticals and the health ministry, a member secretary of the NPPA, the Drugs Controller General of India and the executive director of National Health System Resource Centre.

"There is urgent need to initiate a meaningful dialogue between the government and industry to find amicable solutions and move forward ... A volatile domestic market cannot sustain exports." – IPA

The new committee is expected to recommend measures, among others, to make the pricing policy "more in favor of poor patient's affordable medicare and health security," the ministry notice dated April 6 said. It will also review the scope of the Drug Prices Control Order (DPCO), 2013, and suggest ways to strengthen the regulatory provisions of the order.

The committee will also suggest ways to make the existing mechanism for collecting market-based data on prices of medicines more robust and streamlined and to strengthen the existing pharmaceutical database management system. "Procedural improvement and process re-engineering in NPPA" to ensure better and quicker implementation of government policy (DPCO) and bring greater transparency to reduce litigation and review petitions are also part of its terms of reference. The committee's first meeting on April 6 sought stakeholder comment by May 1 to these proposals.

OUTLIVED UTILITY?

Ironically, much of the ongoing slugfest has played out amid suggestions that the NPPA, in its current avatar, may itself be disbanded. A civil society organization, the All India Drug Action network, is, however, reported to have served a legal notice to certain government functionaries over plans to clip the NPPA's powers, though the latest on this could not be immediately ascertained.

While there's not much clarity on how things may shape on this front, industry predictably says that it's time for the NPPA to go. Danssen Consulting's Dangi refers to the discontinuation of India's Planning Commission and a separate Railway Budget and the proposed abolition of the Foreign Investment Promotion Board as some of the key decisions of the present government to "rein in the bureaucracy". *(Also see "Fosun On Course To Full Indian Clearance For Gland Buyout" - Scrip, 31 Mar, 2017.)*

"NPPA should be the next candidate as it has outlived its utility. It has single-handedly succeeded in retarding the growth of the Indian pharmaceutical industry with its ad hoc policies," he claimed.

Dangi suggests that the NPPA be replaced with an organization like the UK's NICE (National Institute of Health and Care Excellence), whose pricing policies are based on principles of pharmacoeconomics, which does not focus on costs alone but on the cost-benefit ratio for a drug and the value it adds to the patient.

The expert with the foreign firm added that with the DPCO 2013, India had moved to a more predictable and transparent pricing methodology, which curtailed the powers of the NPPA.

"Due to losing its importance from its peak, NPPA has started working to create an environment to move back to cost-based pricing or promote a hybrid pricing model," the expert said.

NPPA chair Singh, though, was recently quoted in the local media as suggesting that he is unwilling to slot the NPPA into "water-tight" definitions like "regulator" or "facilitator" and that the regulator had certainly not outlived its function. He has his fair share of supporters too, with some hailing him as the resolute torch-bearer for keeping drug prices under check.

From the editors of PharmAsia News.
Published online April 11, 2017

Brazil Prepares To Make Its Own Sovaldi As Regulator Opposes Patent Application

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Brazil's medicines regulator, ANVISA, is opposing a patent application from **Gilead Sciences Inc.** for sofosbuvir, the active ingredient of its hepatitis C drug Sovaldi. If the patent office upholds the opposition, Brazil could soon start manufacturing lower cost generic versions of the drug.

Farmanguinhos (the state owned Institute of Pharmaceutical Technology), which filed a petition recommending that the patent be denied, says that if its petition is successful, it will make the drug in partnership with Consórcio BMK, a consortium formed of Blanver Farmoquímica, Microbiológica Química e Farmacêutica and Karin Bruning. Pharmaceutical equivalence and bioequivalence studies are currently underway, says Farmanguinhos.

ANVISA's decision to oppose the application is the first step in the process. INPI, Brazil's patent office, will now examine the application and make the final decision, says Farmanguinhos. ANVISA is able to oppose patent applications under the contentious "prior consent" mechanism, which allows the regulator to object to a patent application on the grounds of public health. Companies have complained that the mechanism leads to delays and confusion, particularly when INPI, the patent office disagrees with ANVISA. Meanwhile, advocates of prior consent argue that it is an important tool for safe guarding public health and guaranteeing access to medicines, permitted under World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights. However, debate about reducing ANVISA's role in the patent application process is ongoing, which the civil society organization, Working Group on Intellectual Property (GTPI) worries could impact the final outcome.

Objections to Gilead's patent application were filed by Farmanguinhos and civil society groups, including GTPI, and have been taken on board by ANVISA. The groups claim that the high cost of Sovaldi means hepatitis C patients are being denied access to the drug, and that patentability requirements have not been met. "Restricting access to medicines because of high prices violates the constitutionally assured right to healthcare," says Farmanguinhos. It adds that granting a patent for an invention that has not fulfilled patentability requirements is illegal and can lead to annulment.

The current price of the drug negotiated with the Ministry of Health is $1,399 per bottle, or $4,197 for a 12-week course of treatment, Gilead told *The Pink Sheet*. "We believe in the National Institute of Industrial Property's (INPI) technical competence to evaluate the patentability of our products. The responsible use of intellectual property is the best way to simultaneously drive therapeutic innovation and ensure access to treatment for all patients," it added. "In Brazil, we are very proud to have worked with the Ministry of Health to enable availability of Sovaldi through the Brazilian public health system, allowing them to significantly scale up treatment in the country and supporting their treatment expansion plans. More than 65,000 patients have been treated with Sovaldi since its launch in April 2015."

Brazil has a high burden of hepatitis C where around 1.6 million people live with the virus. Research claims the drug can be made for just $1 per pill, says Médecins Sans Frontières (MSF), which is supporting the patent challenge. Farmanguinhos says the cost of treatment is prohibitive and that a lower price would allow many more patients to receive treatment.

MSF's Brazil co-ordinator of the organization's Access campaign, Felipe de Carvalho is calling for "a coordinated global effort to ensure effective medicines are available to the largest number of people as soon as possible." He adds that ANVISA's actions are a step towards that. Pressure from around the world is mounting. Egypt, China and Ukraine have already denied patent applications and action is underway in the EU to oppose the same patent that is in dispute in Brazil. *(Also see "Fresh EU-Wide Challenge To Sovaldi Patent Puts The Spotlight On Drug Pricing Again" - Pink Sheet, 3 Apr, 2017.)*.

INDUSTRIAL COMPLEX

The story is not unfamiliar to Gilead, or Farmanguinhos. The firm saw Brazilian state-owned and private manufacturers team together to produce generic versions of its antiretroviral Viread (tenofovir) after a patent application was denied in 2008 *(Also see " Brazil manufactures its own generic version of Gilead's Viread " - Scrip, 22 Feb, 2011.)*. Farmanguinhos was one of the organizations that challenged the patent application. It says its actions led to the denial of the patent, which "benefited thousands of people living with HIV/AIDS and at the same time strengthened Brazil's Economic and Industrial Health Complex." Through this industrial complex, Brazil aims to eliminate the trade deficit for pharmaceuticals by manufacturing priority medicines domestically rather than importing them. The idea is to improve access to healthcare and boost local industry. The challenge to the sofosbuvir patent application will help achieve these ends, says Hayne Felipe da Silva, director of Farmanguinhos.

Published online April 7, 2017

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Global Efforts Intensify In Fight Against Counterfeit Drugs

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Regulatory authorities and the pharmaceutical industry are waging a war against drug counterfeiting on multiple fronts worldwide. Health authorities from around the world recently completed a toolkit of best practices for securing the supply chain, including good manufacturing and distribution practices. In the meantime, an industry official reports progress in spurring interest in the Rx-360 shared audit program.

A World Health Organization representative reports, however, that the counterfeit drug threat is not going away anytime soon.

Drug counterfeiters still target anti-infectives and -malarials in emerging markets more than any other type of drug products, but a new trend is emerging of high-priced counterfeit medicines in "well-regulated" markets such as Japan and Israel. Another new trend is theft of medicines from hospitals.

Regulators and industry representatives discussed some of the challenges in ensuring product quality through the pharmaceutical supply chain as well as several initiatives underway to counteract these threats during a March 28 workshop in Rockville, Md., sponsored by FDA, the US Pharmacopeia and Asia-Pacific Economic Cooperation, an economic forum for the Asia-Pacific region.

At the meeting, regulators announced an APEC anti-counterfeiting "toolkit," which culminates five years of work since the US FDA in 2012 proposed a "Roadmap to Promote Global Medical Product Integrity and Supply Chain Security" to APEC's Regulatory Harmonization Steering Committee.

During the four-day workshop at USP headquarters, regulators from Latin America, Asia and Africa used the toolkit as a reference in guiding discussions on how best practices could have prevented supply chain failures, such as glycerin and heparin contamination incidents. The toolkit has three purposes: prevent, detect and respond to the threat of counterfeit drugs.

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> "At a meeting on antimicrobial resistance, health care workers from Africa and Asia expressed "tremendous concerns about pharmaceutical quality, so this is a real issue that is affecting public health."
> – Jesse Goodman

BEYOND NATIONAL BORDERS

Officials at the workshop emphasized that the problem of counterfeit drugs extends beyond national borders and global approaches are needed to secure the pharmaceutical supply chain.

"This is a really important issue," said USP representative Jesse Goodman. "Several months ago I was at a meeting at the Vatican on antimicrobial resistance, and a lot of on-the-ground health care workers were there, and what was incredible to me was that in Africa and Asia there were tremendous concerns about pharmaceutical quality, so this is a real issue that is affecting public health."

Goodman, a former FDA chief scientist and currently professor of medicine and infectious diseases at Georgetown University, added that "this problem of product quality cannot be solved by FDA alone and by other regulatory agencies alone but it cuts across industry and various sectors. This is a great pilot program in that it connects all these dots and will have a tremendous impact. The goal is to address these supply chain issues."

GLOBAL NATURE OF SUPPLY CHAIN

Ilisa Bernstein, deputy director of the Office of Compliance in FDA's Center for Drug Evaluation and Research, concurred that a single regulatory agency cannot thwart the scourge of counterfeit drugs.

"If a problem product is falsified and found in this part of the world it's going to find its way to the other side of the world. We have to share that information so we can be on the lookout together." Bernstein said.

Bernstein said the toolkit is intended to help regulators and industry detect vulnerabilities as pharmaceutical products move through the supply chain. "There are a lot of threats out there. There is counterfeit, there is diversion, there is terrorism. So when you think about supply chain integrity, it is actually getting to those vulnerabilities and plugging those holes in the supply chain, and this is where we looked for in the roadmap. It was looking at the totality of the lifecycle of the product as it moves through the supply chain."

She said the supply chain security toolkit contains training materials intended to educate regulators and industry members on specific parts of the supply chain, including items such as best practices and guidance documents. It also includes an interactive document that pulls together in one place online information from across the work groups.

APEC senior officials approved the final project report and toolkit at a March 2-3 meeting in Vietnam. APEC, created in 1989, comprises 21 member countries with the goal of promoting trade and creating sustainable economic growth of member economies through policy alignment and economic and technical cooperation.

APEC funded the project for five years but the work group completed it in four. Around 75 representatives from regulators, industry, academics and other stakeholder groups in APEC economies as well as from outside the region participated. They included representatives from Africa, North and South America and the EU.

The US FDA was responsible for "championing this pilot and putting it all together," Bernstein said, adding that "the big deliverable was the toolkit, which has training to educate regulators and industry and it has best practices and guidance documents in order to train others in your economies."

> "If a problem product is falsified and found in this part of the world, it's going to find its way to the other side of the world. We have to share that information," – FDA's Ilisa Bernstein

The team identified 10 priority work areas to ensure the safety and quality of medical products through supply chain security:

- track and trace systems;
- good distribution practices;
- good manufacturing practices;
- good import/export practices;
- clinical and retail pharmacy practices;
- product security;
- detection technology;
- single points of contact;
- online sales;
- and surveillance and monitoring systems.

In each work group, different regulators and industry groups took the lead in developing toolkits. All groups did a gap assessment to identify the current state of supply chain integrity and to assess what is needed for national and regional efforts to identify appropriate areas where standards development and regulatory convergence are needed in APEC and non-APEC countries.

For the GMP work area, for example, the manufacturing practices work group selected these APEC and non-APEC GMPs for study: Brazil, China, EU, India, Japan, US and WHO.

The toolkit focuses on these elements of GMPs the group concluded were directly relevant to supply chain security: supplier and supply chain qualification, supply chain verification, incoming materials checking, yields and reconciliation, outsourcing, and repackaging and relabeling. The gap analyses bridged disparate regulatory requirements in these areas to create a set of best practices.

The toolkit's surveillance and monitoring section urges regulators to report all suspect counterfeit cases to WHO's Global Surveillance and Monitoring System, known as the substandard, spurious, falsely labeled and falsified and counterfeit medical products (SSFFC) data portal.

"This system accepts reports from all over the world on falsified drugs and they send out alerts to the other parts of the world, but that doesn't work unless everyone submits reports," Bernstein said.

EXPENSIVE MEDICINES COUNTERFEITED

Michael Deats, Global Surveillance and Monitoring System group lead, discussed the current reporting trends with counterfeit medicines and why a global approach is needed to address the problem, highlighting the complexity and the interconnected nature of the global supply chain.

Deats reported WHO received 1,371 reports of suspect drugs from regulators in 93 countries since the SSFFC surveillance system was set up in 2013. The data, extracted on Feb. 10, show that 44% of the falsified product reports came from Africa, 20% from Latin America, 19% from Europe, 8% from the Eastern Pacific region, 7% from the Eastern Mediterranean region and 2% from Southeast Asia.

Of the counterfeit products, about 330 were anti-infectives or antibiotics and 300

were anti-parasitics or -malarials. Deats said most anti-malarials are falsified and do not contain any active ingredients. Another 130 of the reported counterfeit drugs were for the nervous system, 120 were genito-urinary products such as emergency contraceptives, and 90 were for the digestive tract.

Deats said weak oversight of the supply chain is a "fundamental cause" of the counterfeit drug problem. "The data is telling us that poor governance leads to substandard and falsified medical products, and that shortages and stock-outs lead to falsified medicines entering the supply chain."

FAKE VACCINES A LINGERING PROBLEM

Deats said fake vaccines are a lingering – and deadly – problem.

In 2016 alone, fake hepatitis B, tuberculosis, polio, and tetanus vaccines were found in Indonesia, leading to 23 arrests. In Niger there were reports of fake meningitis vaccines in 2015, while in 1995, 2,500 deaths were linked to fake meningitis vaccines.

In China, 17 arrests in 2013 were linked to fake rabies vaccines. Fake influenza vaccines were found in the Philippines in 2009, and fake tetanus vaccines were found between 2013 and 2016.

Deats said falsified high-priced drugs is an emerging threat in well-regulated markets.

He said reports are being made of counterfeit hepatitis C medicines such as **Gilead Sciences Inc.**'s *Harvoni* and *Sovaldi*, both expensive treatments: average price for 28 tablets is $32,138 for Harvoni and $29,756 for Sovaldi. Harvoni treats genotype 1 hepatitis C, while Sovaldi treats genotype 2 and both are on WHO's essential drugs list and are considered life-saving drugs.

Counterfeit bottles of Harvoni recently were found in a retail pharmacy in Japan, which Deats called a "very well-regulated market." One bottle was filled with vitamins and another was filled with the less expensive Sovaldi.

In another case, Sovaldi was stolen from a hospital in Pakistan, repackaged as Harvoni and traded through Hong Kong, India and Switzerland before reaching Israel, where a patient noticed the tablets were not the correct shape and color.

NEW TREND: STEALING MEDICINES FROM HOSPITALS

Deats said another emerging trend is health care workers stealing medicines from hospital pharmacies. The motivation, he said, is being underpaid and using the medicines as a "commodity" to trade for food or water.

A 2014 report, "The Theft of Medicines from Italian Hospitals" published by the Joint Research Center on Transnational Crime, documents this trend. It states that "together with counterfeiting, theft of medicines is emerging as the new frontier of pharmaceutical crime. In Italy between 2006 and 2013 one hospital out of 10 registered thefts of pharmaceuticals, suffering on average an economic loss of about €330,000 in each episode."

The report said between 2006 and 2013, Italy's media reported about 68 cases of thefts from hospitals in the country and 51 thefts in 2013 alone, for a total economic loss of at least €18.7m. It also states that "the geography of thefts confirms the hypotheses that southern Italy and the eastern Italian regions are more exposed to thefts of medicines because of the greater activity of organized crime groups."

COMPARING APPLES TO ORANGES

Deats said WHO will continue to use the terms Substandard, Spurious, Falsely Labeled, Falsified and Counterfeit and SSFFC for the time being, but it is renaming the database to better measure the extent of the counterfeit drug problem. He said while one region may call a drug substandard, another may call it unlicensed, and that counterfeit means different things to different people.

He said it has become important to separate these different categories for the purposes of analysis and identifying strategies for the purpose of analysis. A proposed revision calls for three categories: substandard, falsified, and unregistered or unlicensed.

The term "counterfeit" will be dropped. Substandard are authorized medical products that fail to meet their quality standards, their specifications or both. Falsified are medical products with deliberately or fraudulently misrepresented identity, composition or source. Unregistered and unlicensed are medical products that have not undergone evaluation or approval by the regulator for the market in which they're marketed and are subject to conditions under national or regional regulation and legislation.

"There is a need to separate these out because we want to get a better handle on the scope of the issues. There are different approaches to tackle these issues and we need to have the right tools to tackle the issues. Falsified medicines may involve criminal solutions while substandard may involve regulatory solutions. Failing to separate these out makes analysis of the data difficult. We were comparing apples to oranges instead of apples to apples," Deats said.

WHO member states agreed to the new definition in November and recommended it for adoption. The health assembly is expected to adopt the revisions in May.

RX-360 STRENGTHENS RESPONSE TO SUPPLY CHAIN THREATS

Rx-360 CEO Mark Paxton said the pharmaceutical industry also is intensifying efforts to secure the supply chain through shared audits.

Paxton, formerly counsel at FDA's Office of Drug Security, Integrity and Response, said the 2008 heparin tragedy that resulted in 81 deaths in the US galvanized the industry to take a more proactive approach to securing the supply chain. He said that at the time of the tragedy, FDA Center for Drug Evaluation and Research Director Janet Woodcock conducted a meeting with stakeholders and asked, "What are you going to do to address this problem?"

The Rx-360 consortium was formed in 2009 in an industry-led effort to protect the global pharmaceutical supply chain from threats like the heparin adulterant linked to dozens of US patients and deaths in 2008. *(Also see "FDA, Industry Aim to Further Strengthen Pharma Supply Chain Quality" - Pink Sheet, 31 May, 2010.)*

The purpose of the shared audit program is to share costs while enhancing supply chain security.

Paxton said the program has evolved since its inception, including hiring consortium British Standards Institution (BSI) to run audit scheduling and management.

He noted that since bringing in BSI, "the audit forms are a lot more consistent, we

are very form-based and very, very consistent and we keep everything in our database and we have [Corrective and Preventative Action] closeout."

Audit reports originating from the joint audit program may be licensed to members for $2,500 and non-members for $5,000. A list of reports available for licensing is accessible on the website.

Paxton said while Rx-360 has made progress in getting more manufacturers to participate and share audits since its inception, it has yet to achieve its full potential. "We need critical mass and engagement. We are on that path. We don't have critical mass yet but we're certainly working towards that."

He said 400 shared audits have been completed, including 92 requests in the 2017 first quarter alone.

PUBLIC STILL KNOWS LITTLE

Paxton said despite the developments in securing the supply chain, more work is needed.

For example, he said new drugs approved with streptokinase, a thrombolytic medication and enzyme used to prevent heart attacks, contain different levels of the ingredient depending on where they are approved. In Germany, regulators require high levels of streptokinase, while in China regulators can have different, and lower, specifications. However, it is easy for the drug made in China to slip through the borders and be shipped to patients in Germany.

With globalization, this problem only increases, Paxton said.

"What this tells me is that we know absolutely nothing about the supply chain. … The same product can be assayed in China, and I know nothing about that product. That could have been manufactured 100 years ago. People relabel and repackage all the time so I have no idea about that product. … My point is just as with heparin, we don't know about harmful effects until the product reaches the patient. What a sad state of affairs. For all the quality assurance and all the quality-related systems that we put into place, we can't tell anything until it reaches the patient. That is a terrible thing."

From the editors of the Gold Sheet.
Published online April 12, 2017

BIOSIMILARS

Samsung Bioepis's Biosimilar Enbrel 'Substitutable' In Australia As Pfizer Patent Case Is Rebuffed

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> Australia appears to be out on a limb where pharmacy substitution of biosimilars is concerned. For example, no European countries allow it; they prefer to permit switching under the responsibility of the prescribing physician.

Samsung Bioepis Co. Ltd./Merck Sharp & Dohme Australia's biosimilar etanercept product, Brenzys, a version of **Amgen Inc./Pfizer Inc.**'s anti-TNF Enbrel, has been made available under the Australian Pharmaceutical Benefits Scheme as a drug that can be substituted at pharmacy level for the originator.

Meanwhile, in another plus for Samsung Bioepis, an Australian court has denied Pfizer's application for the disclosure of documents on the basis of which it was considering patent infringement proceedings against the South Korea-based company over the manufacturing process for Brenzys.

Brenzys, which has all the indications of Enbrel apart from severe active juvenile idiopathic arthritis, was officially listed on the PBS on April 1, following a recommendation from the Pharmaceutical Benefits Advisory Committee in July last year. In that recommendation PBAC also said that the evidence presented in the company's submission on comparative safety and effectiveness meant that Brenzys could be "a-flagged" as substitutable by pharmacists. *(Also see "Australia's Biosimilar Substitution Policy Under Fire As Etanercept Product Is 'A'-Flagged" - Pink Sheet, 22 Aug, 2016.)*

The Australian Department of Health confirmed that this is only the second biosimilar to be a-flagged. The first was Hospira's Inflectra (infliximab), a version of Johnson & Johnson's Remicade, in 2015. *(Also see "Inflectra To Be First Substitutable Biosimilar In Australia" - Scrip, 21 Aug, 2015.)*

Australia appears to be out on a limb where pharmacy substi-

Shutterstock: Lim Yong Hian

tution of biosimilars is concerned. No European countries allow it; they prefer to permit switching under the responsibility of the prescribing physician. But Australia is not pursuing automatic substitution. The DoH says that while an a-flagged biosimilar can be exchanged for another by the pharmacist, the decision should be made "in consultation with the patient."

And although the pharmacist does not need to refer back to the doctor, the latter can still prevent substitution by ticking the 'brand substitution not permitted' box on the prescription form.

Not all biosimilars will be a-flagged – decisions will be made on a case-by-case basis. Finox Biotech's Bemfola, a biosimilar version of **Merck Serono SA**'s Gonal-F (follitropin alfa), was listed on the PBS in August 2016, but PBAC did not recommend a-flagging because of differences in strengths, number of pens per pack, and maximum quantities between the products. "Substitution at the pharmacy level would have been difficult from a practical perspective," the department said.

A-FLAGGING CRITERIA

As a general rule, when determining a-flag status, PBAC will consider a number of criteria including the following:

- If there are data to suggest significant differences in clinical effectiveness or safety compared with the originator product.
- If there are identified populations where the risks of using the biosimilar product are disproportionately high.
- The availability of data to support switching between the originator product and the biosimilar.
- The availability of data for treatment-naïve patients being started on the biosimilar.

PFIZER CASE

In its legal action, Pfizer had applied for the discovery of confidential documents from Samsung Bioepis relating to the manufacturing process for Brenzys in order to decide whether to bring proceedings against Samsung Bioepis for the infringement of method of manufacturing patents on Enbrel, according to law firm Bird & Bird.

Pfizer claimed among other things that Brenzys must have been manufactured using the patented method, particularly given that the glycosylation profiles of the two products were very similar, but the judge said that while the end products were similar, this did not mean the methods were.

According to Bird & Bird, Pfizer also submitted that since Samsung Bioepis did not deny in correspondence or during the proceedings that the Brenzys manufacturing process involved the patented method, "the court should draw an inference that this was the case". The judge, however, "noted that the inference was available to Pfizer, nevertheless it would be inappropriate to draw the inference in the present case".

Overall, the judge ruled that Pfizer's contentions did not satisfy the threshold for "reasonable belief" that Pfizer might have a cause of action, and therefore refused the company's application for discovery of the documents in question.

Pfizer's failure to obtain an order for discovery shows that the owner of a biologic manufacturing process patent "will need something more concrete than the fact that the biosimilar has the same characteristics as the biologic to ground a reasonable belief of a patent infringement claim," Bird & Bird observed.

"The case demonstrates the difficulty for patentees trying to establish infringement of process claims, in the absence of co-operation by production of documents by the alleged infringer. Patentees will need to consider very carefully how they formulate and evidence their belief in the use of the patented process before seeking discovery in such circumstances," the law firm concluded.

From the editors of Scrip Regulatory Affairs. Published online April 11, 2017

FDA's NDA And BLA Approvals: Ingrezza

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				
Neurocrine	*Ingrezza* (valbenazine)	Treatment of tardive dyskinesia.	P, 1	4/11/2017

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

FDA Should Call Last Round For OTC Hangover Indication, Cmte. Suggests

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"Hangover is well known to everyone, well known to the general public as the morning after the night before."
– CHPA consultant Damaris Rohsenow of Brown University's Center for Alcohol and Addiction Studies

Including hangover as an indication for OTC monograph drugs could be more problem than remedy by contributing to misuse of antacid/analgesic and aspirin/caffeine nonprescription products, an FDA advisory panel concludes.

Comments from members of the Nonprescription Drug and the Drug Safety and Risk Management advisory committees during a joint meeting of April 4 could push FDA toward dropping hangover as a monograph indication.

The committee did not vote on the issue. But members raised a variety of issues including consumer's self-diagnosis of hangover, rather than more serious conditions such as alcohol withdrawal or other symptoms such as upset stomach, and potentially greater risk of bleeding for those using alcohol and taking analgesics.

Antacids for conditions such as heartburn, nausea, fullness, belching, gas, acid indigestion or sour stomach are marketed under FDA's internal analgesic and antacid monographs, which are in final status. Some products with a specific hangover indication are marketed under the internal analgesic monograph.

Monographs for overindulgence and stimulant products currently include a specific hangover indication. While products are available under those monographs, the policies remain only at the "tentative final" stage. They are caught up in FDA's long-stalled process of conducting rulemakings for finalizing proposed monographs or amending final monographs with additional ingredients or indications.

FDA scheduled the NDAC and DSRMAC meeting for advice on whether hangover is appropriate as an OTC indication based on findings by the agency's advisors, made in 1982, that antacid/analgesic combinations were generally regarded as safe and effective for minor pain and upset stomach associated with overindulgence in food, alcohol or booth, and aspirin/caffeine combinations were GRASE for hangovers. *(Also see "OTC Hangover Remedy Safety On Tap For FDA Advisory Committees" - Pink Sheet, 3 Mar, 2017.)*

Karen Mahoney, deputy director of FDA's Division of Nonprescription Drug Products, explained to the panel that the division has not determined whether to include hangover as an indication or antacid/analgesic and aspirin/caffeine as accepted combinations in final monographs.

"There is still a need for information to help the FDA make its decision and write final monographs. The input that the committee gives us today will be very beneficial as we attempt to finalize those monographs," Mahoney said.

FDA sought the panel's comments on the hangover indication but did not seek a formal voting recommendation.

The panel made one voting recommendation, advising that antacid/analgesic combinations do not meet the OTC monograph threshold for safe and effective ingredient combinations. *(Also see "What's Next For Antacid/Analgesic OTCs After Negative US FDA Panel?" - Pink Sheet, 4 Apr, 2017.)* Concerns about a potential link between aspirin or acetaminophen use and serious internal bleeding prompted FDA's inquiry on this topic.

A spokeswoman said DNDP has not set a timetable for its next step in determining whether hangover will remain in the monograph.

HANGOVER SYMPTOMS VARY

Research presented for the Consumer Healthcare Products Association and presentations by **Bayer HealthCare LLC**, maker of *Alka-Seltzer* products for acid indigestion and minor head and body aches, and *Blowfish* aspirin/caffeine hangover remedy firm Rally Labs LLC attested to the safety and efficacy of OTCs marketed under monographs and to hangover as an

Shutterstock: Rachaphak

indication that is easily self-identified by consumers.

"Hangover is well known to everyone, well known to the general public as the morning after the night before," said CHPA consultant Damaris Rohsenow, of Brown University's Center for Alcohol and Addiction Studies, during her presentation on hangover treatment studies she has conducted.

Rally Labs founder and CEO Brenna Haysom pointed out that 90,500 consumers conduct online searches for hangover each month, slightly less than searches for headache and heartburn but more than cough and congestion. "A large number of consumers are actively trying to treat these symptoms," Haysom said.

The monograph indication for treating hangover, she added, "confirms the safety and effectiveness of the product."

The overindulgence TFM defines hangover as "a condition consisting of a complex of symptoms involving the gastrointestinal, neurologic and metabolic systems that follow recent excessive alcohol ingestion," and say the symptoms may include nausea, heartburn, thirst, tremor, disturbances of equilibrium, fatigue, generalized aches and pains, headache, dullness and depression or irritability.

Rohsenow said her research limits hangover symptoms to four general areas, fatigue, thirst, nausea and head and body ache. "It's well known to the public. There's no mystery there," she said.

MARGIN FOR ERROR A CONCERN

Physicians, pharmacists and medical researchers on the panel, however, did not agree.

"If I don't understand hangover … is the average consumer going to be able to differentiate hangover from chronic alcoholism or alcohol withdrawal?" said temporary DSRMAC member Timothy Lipman, a clinical medicine professor at Georgetown University and former head of GI-hepatology-nutrition section at the Washington VA Medical Center.

A second temporary DSRMAC member, Steven Solga a gastroenterologist and a clinical medicine professor at the University of Pennsylvania Perelman School of Medicine, observed that his and others'

HANGOVER AND OTC MONOGRAPHS

These four monographs were part of the advisory committee discussion:

- **Internal analgesic:** status is final, hangover indication included
- **Antacid:** status is final, hangover indication not included.
- **Overindulgence:** status is tentative final, hangover indication included
- **Stimulant:** status is tentative final, hangover indication included

HANGOVER OR WORSE?

Allowing drugs to be labeled as hangover remedies also could contribute to consumers using analgesics while still drinking or with alcohol still in their systems, which increases risk of liver damage, and could obscure conditions consumers may have other than pain and upset stomach from an isolated event of drinking too much, researchers suggest.

"We are very concerned about products that are marketed for hangovers that contain acetaminophen or aspirin," said Megan Polanin, a senior fellow at the National Center for Health Research, during the open public hearing period of the meeting.

Polanin, who works on NCHR's patient advocate training project and manages its Affordable Care Act project, noted that many consumers are not aware that acetaminophen isn't indicated as a hangover remedy, and they aren't likely to learn when they need the remedy.

"A person who has been drinking enough to experience a hangover or to expect a hangover is not likely to be in condition to be able to read and understand an OTC drug label," she said.

Timothy Lipman, a temporary DSRMAC member and a clinical medicine professor at Georgetown University, also observed that informed decisions on medicine use don't follow high alcohol consumption.

"At 8 a.m. I don't care whether I'm still intoxicated or hungover, I just want get rid of my headache and my lousy feeling," said Lipman, former head of GI-hepatology-nutrition section at the Washington VA Medical Center, in describing a likely circumstance.

Polanin also suggested FDA change acetaminophen- and aspirin-containing OTC labeling from the current warning against using when consuming three or more alcoholic drinks in a day to also advise against using after any episode of heavy drinking.

"It is important to keep in mind, however, that many people do not consider drinking five or more drinks at a time to be heavy drinking or even binge drinking," she added.

research shows that short-term use of aspirin does not directly cause bleeding but reacts with other chemicals in the body to create conditions susceptible to hemorrhaging. However, persons who need help for a hangover could already be susceptible to internal bleeding.

"I'm not sure anybody waking up with hangover is really going to think about it that clearly," said Solga.

Others on the panel pointed out that consumers may be using antacid/analgesic combination OTCs for what they consider a hangover, but they could be experiencing only minor pain or only upset stomach. Through such misuse, consumers unnecessarily are using aspirin or other analgesics, increasing their potential risk for stomach bleeding; or antacids, which when over-used can cause constipation, diarrhea, slower breathing due to a rise in blood pH or infections due to hyper-suppression of stomach acids.

Rohsenow's research, conducted with Boston University School of Medicine professor Jonathan Howland, shows that treating a hangover might not require a pain reliever and stomach aide.

Their presentation slides stated, "People may not get all of these symptoms each time they have hangover," and "One person might want to treat headache but not stomachache or vice versa."

NDAC member Neil Farber, a general internist and a professor of clinical medicine at the University of California, San Diego, noted that while "medications need to be generally safe and effective," label indications and directions determine whether drug ingredients are used appropriately.

Linking drugs, in single- or combination-ingredient formulations, to an indication requires accurately defining a condition through symptoms, but FDA's initial monograph advisors might have been off the mark in the TFM for overindulgence and hangover indications, said Farber.

"Do we know what the definition of over-indulgence is?" he said. "Are we actually asking the same question as hangover?"

Mahoney pointed out that whether consumers appropriately use OTCs indicated for hangover is a critical part of FDA's evaluation of the indication. Like scientific information on drug ingredients and indications, research findings on self-selection of OTCs have changed since the monograph process began and the TFMs FDA is reconsidering were proposed.

> "Do we know what the definition of overindulgence is? Are we actually asking the same question as hangover?" – Neil Farber

"These recommendations were made a long time ago and science has progressed greatly. Not only clinical science, but also our understanding of how important consumer comprehension is," Mahoney said.

DATA UNIMPRESSIVE OR UNDERREPORTED?

The science about potential risks from allowing OTC drugs to use a hangover indication isn't swaying the industry, though.

From 1969 through July 2016, FDA's Adverse Event Reporting System show 20 cases of serious bleeding potentially linked to antacid/aspirin use, though 80% of those – 16 – included risk factors such as age, history of stomach ulcers or alcohol abuse and use of contraindicated drug.

FAERS data also show no reports of serious bleeding potentially linked to use of aspirin/caffeine products indicated for overindulgence or hangover, according to the Center for Drug Evaluation's meeting presentation.

Rally Labs' Haysom stated the firm has not received any serious adverse events reports from consumers, though she committed to later providing the panel with information on other AERs the New York firm has received.

The industry's non-voting representative on the panel, Roger Berlin of 1,681 Consulting LLC in Philadelphia, noted the 20 reports are spread across 44 years and "just about all of the cases are confounded."

"If you look at the data FDA has put together, it's not necessarily compelling," said Berlin, a physician, an expert in global prescription and nonprescription pharmaceutical development and a former pharma firm executive.

Like Mahoney, other CDER officials acknowledged the comparatively small number of reports of serious bleeding linked to antacid/aspirin products, but they also told the panel they expect many incidents are not reported.

"It's not a lot of reports but we have reason to believe that under-reporting could be significant for this," said Christopher Jones, director of CDER's Office of Pharmacovigilance and Epidemiology.

Under-reporting of internal bleeding could stem from physicians and other health care professionals not considering it a condition meriting an adverse event report or consumers simply not being aware of FAERS or that they can contact product marketers.

The small number of reports "should not be interpreted as a lack of risk for serious gastrointestinal bleeding," said Ali Niak, medical officer for CDER's OPE and its Office of Surveillance and Epidemiology.

"If I see someone with GI bleeding from aspirin, I'm not going to report it to the FDA even though I should," added Niak, also a physician.

"I, as a practicing physician, also don't report these cases," said DSRMAC member Niteesh Choudry, a Harvard Medical School professor and Brigham and Women's Hospital physician.

From the editors of the Tan Sheet.
Published online April 10, 2017

Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
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
Development of antibacterial drugs that treat a single species of bacteria when the target species infrequently causes infections	Antimicrobial Drugs	April 13

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