INTERVIEW: New EFPIA President On The Future Of Innovation

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The future of pharmaceutical innovation lies in a collaborative, multidisciplinary approach where all stakeholders work together in a more “connected” health care environment, making full use of human and cell biology and resources like real world evidence, big data and advanced analytics to develop treatments that address the fundamental causes of disease.

Greater cooperation and dialogue is the key to tackling issues like the affordability of new drugs in the face of health care system constraints, but a major challenge in the future will be to ensure that Brexit does not lead to more complexity and fragmentation in the European health care environment.

That is the view of Jean-Christophe Tellier, CEO of UCB and, since 27 June, the new president of the European pharmaceutical industry federation, EFPIA. Speaking to the Pink Sheet on the day before his appointment, Tellier said that his priority during his two years at the EFPIA helm would be to bring together the often disparate expertise across Europe to “deliver the best possible outcome for the patient.”

‘CONNECTED HEALTH CARE’

Tellier said that while all stakeholders wanted to develop new therapies that provided the best patient outcomes, too often they were working in isolation “and sometimes even against each other. Connected health care is necessary – we have to work with the different stakeholders and by working together and engaging in dialogue we will find a way to deliver more to the patient.”

How would this be done? “We don’t start from scratch,” Tellier said. “There are many great examples of collaborations across Europe right now, but either these are mainly based on different individuals or organizations working together, or they have certain local limitations. I don’t feel that today these are yet at the scale that we need, but we can start from these projects and these individual pilots to build for the future.”

As well as heading up UCB and EFPIA, Tellier also chairs the Innovative Medicines Initiative, a joint enterprise between EFPIA and the European Commission. The IMI has just announced its latest call for research topic proposals, which include advanced therapies such as CAR-T cells and gene therapy. (Also see “New IMI Funding For EU Research Into ATMPs, Health Outcomes & Drug Info” - Pink Sheet, 26 Jun, 2019.)

He said the IMI was a good example of the kind of collaborative approach that was needed to take forward innovative drug R&D, and that it could act as a model for future ventures. “One of the key elements of the IMI was the recognition that some topics cannot be solved by one actor, one stakeholder, whatever their size or relevance,” he said.

The other key component is the resources in kind that the pharmaceutical industry was asked to bring to the IMI. “We had skin in the game, and brought our people in, and that made it possible for people who don’t normally have a lot of opportunity to work together to really build some projects together. So I think those are two very positive elements we can build on.”

BIG DATA

A further advantage of the IMI approach, he said, was that it allowed economies of scale to be achieved at the European level, for example in the area of big data. One IMI project, EHDEN (European Health Data & Evidence Network), is aiming to create a common database across different EU countries.

EHDEN, a consortium involving 22 partners, is led by the Erasmus Medical Centre and has 11 pharma firms on board. It is intended to harmonize the anonymized health records of more than 100 million people, Tellier noted.

He said the problem at present was that each country in Europe has its own data collection system and its own patient data, and that making it possible for people who don’t normally have a lot of opportunity to work together to really build some projects together. So I think those are two very positive elements we can build on.”

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and it is “very fragmented. It is impossible to leverage the potential value of technology, advanced analytics and artificial intelligence if we don’t have access to a large amount of data. This is really an area where working at the European level helps a lot.”

Asked what he saw as the key areas of innovation in medicine in the coming years, Tellier said much would depend on exploiting the opportunities opened up by the sequencing of the genome. Human and cell biology would be “the future source of multiple innovations,” particularly in chronic diseases, where “currently we are treating only the symptoms” and where cures might eventually be found.

“Today chronic diseases are treated chronically,” Tellier observed. “We can manage that with the current framework, but think about an intervention that is done once and the patient is treated for the rest of their life. How do you evaluate the fair value of that and how you will pay for it over time? There are a lot of questions that will not be solved independently from each other.”

“This for me is also a good example in terms of stimulating a more connected environment – we need to anticipate, to talk to different stakeholders.”

REGULATORY CONVERGENCE?

Of course, once these new therapies have been developed, they must pass the regulatory review hurdle. The regulators need to be comfortable with these new treatments, and they don’t always handle innovation in the same way. New drugs are frequently approved in one country or region but not in the other; indeed, there have been suggestions that some companies prefer to take their new drugs to the US Food and Drug Administration first for example, rather than the European Medicines Agency.

Tellier said it was up to each company to determine its regulatory filing strategies, as there were “a lot of elements to be taken into consideration.” However, he did note that “what is important for us as an industry is to ensure there is more and more convergence among agencies so that they can see the challenges we have in a more aligned way.”

He said it was important to “ensure we have the best possible agency here in Europe to support competition and patient access.” What was needed was a “dynamic regulatory assessment” that involved tools like real world data, new kinds of clinical trials beyond the randomized controlled model, and biomarkers to allow the selection of suitable patient populations. “We are willing to work with EMA to facilitate this dialogue and translate advances in science more quickly into regulatory assessments.”

“It is impossible to leverage the potential value of technology, advanced analytics and artificial intelligence if we don’t have access to a large amount of data. This is really an area where working at the European level helps a lot.”

AFFORDABILITY OF NEW THERAPIES

Then there is the question of getting approved drugs to patients – and here too Tellier sees benefits in a collaborative approach.

He said it was important to ensure that the affordability challenges of health care systems are addressed. “It is in our interests as a pharmaceutical industry that we work with health care systems that are sustainable in the future.” Rather than focusing on the 20% of European health care spending accounted for by medicines, he said, it was important to look at health care investment overall and “evaluate what will in the future be the impact of new medicines on different components of spending, and how to better allocate resources towards the greater value.”

He noted again that the paradigm would change for chronic disease, where future treatments would be much shorter. “How do we create the possibility for the systems to afford payment? I do feel that understanding what is coming, explaining the pipeline and the evolution of the science to stakeholders, including payers, regulators, hospitals, and so on, is very important to help them prepare – we will have to build a new platform and find a new way to manage these patients.”

In similar vein he welcomed the move towards more joint health technology assessments across the EU – an area where EFPIA has previously advised some caution. (Also see “EFPIA On How To Make Cross-Country Collaborations Work” - Pink Sheet, 23 Jan, 2019.) “It would help from our perspective to align clinical assessments, to accelerate evaluations, and to avoid waste in the system and duplication of tasks to ensure investments provide value.”

He stressed, though, that it was only the clinical assessment that would be done jointly, and that in the end each EU member state would continue to control access and reimbursement. “I see value in that, and no negative components.”

Of course there had to be one jarring note in this harmonious vision: the Brexit factor, and particularly the possibility of the UK leaving the EU without a deal at the end of October – a prospect that is anathema to the UK industry bodies, the ABPI and the BIA. (Also see “UK Pharma Decrees Govt’s Latest No-Deal Brexit Planning” - Pink Sheet, 27 Jun, 2019.)

Tellier said that while for most sectors the impact of Brexit would be economic, for the life sciences sector it was “patient safety and the continuity of health care that is the main concern.” It was important, he said, to avoid any supply interruptions.

“We would of course prefer to have a deal,” Tellier said. “In the short term we are prepared, building stock to prevent risk of interruptions. But in the long run, the key challenge for us is making sure that Brexit doesn’t create additional complexity or fragmentation.”

He stressed the importance of somehow keeping the UK in the innovation “loop” once it leaves the EU. He said EFPIA was trying to stimulate a more connected environment, “so whatever the post Brexit situation, it will be very important to keep the UK in this connected health care network.”

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UK Pharma Decries Govt’s Latest No-Deal Brexit Planning

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The UK government says it is taking more steps to help guarantee the supply of medicines and medical products in the event of a no-deal Brexit at the end of October, including the provision of “express freight” capacity for products that require “urgent delivery.” It is also expanding its advice on contingency planning to cover products other than prescription medicines, including over-the-counter drugs, “specials” and parallel imports and exports.

Noting that “significant disruption” to supplies would be expected for six months after a no-deal exit, the government has asked companies to take more action to ensure continuity of supply, such as rerouting freight away from the channel crossings between the UK and French ferry ports, and ensuring their logistics and supply chains are ready for new customs and border requirements.

In a written statement to parliament, Cabinet Office minister David Lidington said the Department of Health and Social Care was “starting the process of setting up an express freight contingency arrangement” that would be “an urgent measure” for products requiring delivery within a 24-48 hour timeframe if the UK leaves the EU without a deal.

The arrangement was part of the DHSC’s “multi-layered approach,” Lidington said. This included rerouting medical supplies from the short strait crossings, finding extra warehouse space, stockpiling of medicines, building up buffer stocks, clarifying regulatory requirements, helping traders to have the necessary paperwork in place at the border, and strengthening processes used to deal with shortages.

However, he stressed that the government would “only pay for capacity as and when it is needed and used,” and that the DHSC would be writing to industry to set out further details of the preparations.

UK pharmaceutical and life science industry bodies were not overly impressed. Steve Bates, CEO of the BioIndustry Association, noted that the government’s program was different from that prepared for the original Brexit date of 29 March, both in terms of freight support and what was being asked of industry.

“Our sector has already endured considerable disruption, duplication and uncertainty, and invested significant time, effort and resource with little government support, Bates said. “There is now an additional requirement around border paperwork which brings additional burden, especially for smaller companies, as much of this work is contracted out work.”

He said that while the government had listened to industry about the need for extra freight capacity, there were now only 127 days until a possible no-deal Brexit, and making changes at short notice was not easy for his sector.

“Supply chains are complex, integrated across Europe and regulated at every stage. Many products are temperature-controlled, and some deliveries can’t exceed three days or deviate from approved storage conditions. Some products have a short shelf life and can’t be stockpiled and must take longer than 127 days to produce,” Bates declared.

The chief executive of the Association of the British Pharmaceutical Industry, Mike Thompson, said companies had been doing “everything in their power” to prepare for Brexit, including stockpiling, duplication of testing facilities and planning for alternative supply routes where possible.

“But some things are outside of their control,” Thompson said. “Additional Government secured freight capacity was key to company planning for a ‘no deal’ in March and this must be available to companies again as they prepare for the end of October,” he declared.

He said companies would be pleased the government was taking steps to put this capacity in place again, and that they would await further information about how this would work in practice. However, he said, it was “extremely challenging for pharmaceutical companies to be continually preparing for a ‘no-deal’ Brexit. Leaving the EU with a deal in place remains the...
best way to minimise any potential disruption to medicines supplies."

**DUPICATION OF RED TAPE**

Bates said a no-deal Brexit would mean “the biggest disintegration in a lifetime of the complex regulated medicines market across Europe in terms of regulation, cross border movement of goods, comparative pricing and intellectual property.”

He also criticized what he saw as more duplication of red tape for the life sciences industry, “despite assurances from ministers that this would not happen.” The government’s no deal Statutory Instruments had introduced elements that would “adversely impact both industry and patients,” Bates asserted.

For example, he said, industry did not understand the requirement for an additional oversight system to verify Qualified Person certification of investigational medicinal products imported from EEA countries that was included in the Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019. “If there is a ‘no deal,’ BIA calls on the Government to immediately review these and other regulations,” he declared.

He said industry also needed to know whether the two candidates for the Conservative Party leadership – Boris Johnson and Jeremy Hunt – supported the government’s approach to no-deal Brexit planning.

**MORE DETAILS ON SUPPLY ARRANGEMENTS**

More nuts-and-bolts detail of the government’s latest thinking on Brexit and medicines supplies was laid out in a letter to pharmaceutical and medical products firms from Steve Oldfield, chief commercial officer at the DHSC. He noted that some of the contingency recommendations – such as stockpiling needs – were originally made in advance of the 29 March deadline, particularly with regard to possible holdups of products on the “short straits” crossings between the French ports of Calais, Dunkirk and Coquelles and the UK ports of Dover and Folkestone.

“While the predicted flow rate across the short straits has improved slightly since 29th March, significant disruption would be expected for six months following a no-deal exit, with the most severe period being the first three months,” he declared.

Bates said industry needs to know whether the two candidates for the Conservative Party leadership – Boris Johnson and Jeremy Hunt – support the government’s approach to no-deal Brexit planning.

He advised companies to ensure their preparedness plans contained a mix of the following measures, depending on each firm’s specific circumstances:

- Secured capacity for rerouting freight away from the short straits after no-deal exit day, in order to avoid the worst restrictions on product flow.
- Stockpiling products above and beyond business-as-usual inventory levels; as a default, this is recommended as an additional six weeks’ stock, the same as for the March deadline. Where stockpiling is not feasible, for example medical radioisotopes or products with a short shelf life, companies should make alternative air freight plans.
- Assurance on the readiness of a company’s logistics and supply chains to meet the new customs and border requirements for both import and export (“trader readiness”).

Where companies have already made plans containing these three elements, he said, “we will continue to work with you on ensuring these are robust, and help you deal with any specific product issues by exception.”

In the coming days, he said, companies would be asked to “provide information at product level, focused on the minimum key data set necessary for assurance of the programme.” This would build on information from the 29 March exercise, including stock levels that are expected to be held on 31 October, and plans for re-routing away from the short straits.

Oldfield also said that while this advice is aimed mainly at suppliers of prescription-only and pharmacy medicines with an EU touchpoint, the government had also been considering the implications of the latest border planning assumptions on suppliers of other categories of medicines, such as critical general sales list drugs, unlicensed medicines, “specials,” and parallel imports and exports, as well as on UK manufacturers of products where raw materials may come from or via the EU or the European Economic Area.

“While a combination of stockpiling and re-routing, together with trader readiness, would also be advisable for these products too, we will be engaging separately with companies on their contingency plans over the coming weeks,” he said. He added that the department would continue to provide warehousing capacity and would “keep industry updated on how they can access this additional storage in advance of 31 October.”

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REGULATORY UPDATE

PEDIATRIC CANCER: US FDA Will Take ‘Rational’ Approach To Requiring Combination Studies

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The US Food and Drug Administration intends to take a measured approach to deciding what combinations of therapies should be investigated when new pediatric cancer study requirements take effect in August 2020.

“I think we want to be as rational and as clinically and scientifically appropriate in the decision-making about when to proceed, how to proceed with early evaluation of novel agents and early evaluation of novel agents that are going to require combinations with something else,” the FDA’s Gregory Reaman said at a 20 June meeting of the Oncologic Drugs Advisory Committee’s pediatric subcommittee.

Applications for novel drugs and biologics submitted after 18 August 2020 must include reports on a “molecularly targeted pediatric cancer investigation” if the product is intended to treat an adult cancer and directed at a molecular target that the FDA determines to be substantially relevant to a pediatric cancer. This requirement was established under the RACE for Children Act provisions in the FDA Reauthorization Act of 2017.

While the RACE provisions are aimed at early evaluation of targeted agents in pediatric cancers, they do not specifically address the issue of combinations, said Reaman, associate director for pediatric oncology in the Oncology Center of Excellence.

“Despite the fact that it doesn’t necessarily address combinations, when there is information that’s available from either preclinical data or from limited adult clinical data, and if one or more of the agents in the combination is new, then there could be a requirement for an early evaluation,” he said.

“At the same time, when we evaluate new agents that might be coming in, as part of an initial Pediatric Study Plan, that are being developed for an adult cancer and there’s some lack of clarity about what the combination might be, we would probably defer decisions about requiring early evaluation until there’s more definitive data to suggest that the presumed mechanism of action on a pediatric tumor is also going to require an additional agent and what that agent should be,” he said.

GUIDANCES DELAYED BY CLEARANCE PROCESS

How the FDA will prioritize pediatric studies for multiple agents in a class, as well as combinations of agents, has been a lingering concern for industry and investigators as the agency works to implement the RACE provisions.

As required by the statute, the agency has developed lists of molecular targets that are substantially relevant to pediatric cancers, potentially triggering study requirements, and those that are not relevant. (Also see “US FDA’s Pediatric Cancer Targets List Spurs Questions On Breadth, Prioritization” - Pink Sheet, 26 Apr, 2018.) The agency intends to hold semi-annual public meetings to get input on recommendations for target list additions or deletions, Reaman said.

Findings presented at the American Society of Clinical Oncology’s recent annual meeting could signify an increase in the range of targets considered relevant to pediatric oncology. (Also see “Pediatric Oncology Advances Could Prompt More FDA-Required Studies” - Pink Sheet, 16 May, 2019.)

The agency also is developing draft guidance for industry. Guidance on implementation of the FDARA provisions was required by statute, with the final version due by 18 August 2019. The agency has said a second guidance will be a Q&A document.

“When there is information that’s available from either preclinical data or from limited adult clinical data, and if one or more of the agents in the combination is new, then there could be a requirement for an early evaluation.”

– FDA’s Gregory Reaman
Another unknown is whether novel combinations of immunotherapies can induce responses in pediatric cancers, as some preclinical models have suggested, she said.

“There’s reason to have continued interest in this class of agents, but we’re left with a conundrum, because there are hundreds of potential combinations,” Mackall said, adding that the RACE Act provisions will make many more of these agents available for study.

“I get calls all the time now from companies with their immunomodulator that they want to study in children, which is good. We’re happy to have companies interested. But the truth is we cannot study all of them and so now we have to become, I think, much more sophisticated with our ability to prioritize what trials are done in children,” she said.

A NEED TO PRIORITIZE …

The FDA convened the ODAC pediatric subcommittee to gather input on potential additions to, and deletions from, two of the lists of substantially relevant targets: cell lineage-based targets; and tumor microenvironment and normal immune cell targets.

“Checkpoints inhibition as a single therapeutic maneuver has limited impact in sporadic pediatric cancers,” she said, citing a need to “think hard about what are the trials that should be done in the future with these agents.”

Mackall said there are ongoing studies with combinations of immune checkpoint inhibitors that have resulted in sporadic responses. In addition, a clinical trial testing the hypothesis that combination checkpoint therapy may be effective in pediatric cancers that are stratified as “hypermutant” will be launched in the Pediatric Cancer Immunotherapy Trials Network in the coming months, she said.

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– Stanford’s Crystal Mackall

The agency also asked the committee for recommendations on how best to evaluate and prioritize combinatorial approaches to evaluating agents directed at targets on normal immune cells.

Guest speaker Crystal Mackall, a pediatric oncologist and director of both the Stanford Center for Cancer Cell Therapy and the Parker Institute for Cancer Immunotherapy at Stanford, described the disappointing efficacy results to date in pediatric trials of single-agent immune checkpoint inhibitors. “Checkpoints inhibition as a single therapeutic maneuver has limited impact in sporadic pediatric cancers,” she said, citing a need to “think hard about what are the trials that should be done in the future with these agents.”

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… BASED ON STRONG PRECLINICAL OR ADULT DATA

Combinations that demonstrate efficacy in preclinical models that mirror the low mutational burden of pediatric solid tumors in an intact immune system should be prioritized, Mackall said, although she acknowledged that more of these types of model systems are needed. She also called for prioritizing combinations that demonstrate efficacy in adult low immunogenicity tumors.

Mackall’s suggestions were favorably received by panel member Malcolm Smith, associate branch chief for pediatrics at the National Cancer Institute’s Cancer Therapy Evaluation Program. He cited the need for strong preclinical or adult data, a clear understanding of mechanism of action, and a hypothesis-driven approach before testing combination regimens in pediatric patients.

Noting that the pediatric research community’s primary interest will be in engineered T-cells and combinations involving bispecifics, he said: “If we really have a tumor that doesn’t have neoantigens and it appears to be invisible to the immune system, before we start making combinations I think we really need some evidence that there is something that is being recognized,” Smith said. “Before we get deep into combinations, I think there should be a clear understanding this is what we’re targeting with this combination, that it will allow you to use this to recognize it.”

Adult cancer studies of combinations are “where we’re going to learn if some of these new concepts [of] stimulating new approaches to recognizing cold tumors may play out,” he said. “I think until we see really good signals there that we’re not going to be able, absent extraordinary preclinical data, to really make good advances in pediatric cancer.”

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SAN DIEGO – The US Food and Drug Administration expects that its study to reproduce the results of randomized controlled trials using real-world evidence will fail to replicate in some instances – a result that could drive a better understanding of how to use claims and other real-world data.

Asked during a 25 June session of the DIA annual meeting, Center for Drug Evaluation and Research’s David Martin acknowledged that the agency is not expecting complete replications.

Slides that Martin had prepared state that “probability of regulatory agreement in the absence of bias should be in the 80-90% range” for a real-world evidence (RWE) study aiming to duplicate a randomized controlled trial (RCT) that showed “significant effects.” The presentation was less clear about how much replication the agency is expecting for RCTs without significant effects.

“All I would say that’s premature for me at FDA to talk about that in more detail than that,” Martin said. “But I think the general message that is clear is, obviously in the absence of bias, there is a statistical expectation that it would still not be 100% duplication. And I’m comfortable saying that.”

Martin, the associate director for RWE analytics in CDER’s Office of Medical Policy, did reveal that FDA has still not settled on the terminology to describe the replication effort. “By the way, my first disclaimer is we haven’t really decided,” he said, referring to the ubiquitous disclaimer slide that makes up the second screen of every presentation at the four-day meeting.

“Some believe that duplication is perhaps a better term than replication since there’s some inherent differences,” Martin said. “We don’t have a strong opinion, I don’t think. Feel free to call it whatever when you wish.”

FDA is funding a study with the goal of creating approximately 30 retrospective trial replications by March 2020 as part of a requirement of the 21st Century Cures Act. (Also see “Real-World Data Could Get Boost From Trial Replication Project” - Pink Sheet, 26 Apr, 2018.)

The study’s lead investigator, Harvard Medical School’s Jessica Franklin, told the DIA session that complete replication wouldn’t even be the best outcome. “We learn the most when we don’t replicate, because then we really have to dig in and figure out why,” she said.

“We certainly will for all of the clinical trial replications be doing lots of sensitivity analyses, whether we replicate or not. Because if we did replicate, how robust is that finding? Does it fall apart when you change one little thing? But then if we don’t replicate, can we figure out why?”

For the primary analyses of the RWE studies, the project is using the same inclusion/exclusion criteria as the RCTs did, “but we’re not actually weighting to the trial population,” Franklin noted. “And then with sensitivity analyses, we will do that to try and explore if these smaller differences between our population and the trial population could explain the differences.”

The study will also consider other sensitivity analyses like changing follow-up time and different definitions of inclusion and exclusion criteria, because “in all of our attempts to replicate, we’re having to make hundreds of choices that are as clinically and epidemiologically informed as possible, but certainly another set of investigators would likely make many different decisions than us,” Franklin said.

“My hope is that anybody else who’s interested … if they want to look at our documentation that’s available on clinicaltrials.gov and go and implement their own replication, that that would make me extremely happy. And if they’re able to replicate in places where we can’t, that would be great, because we would all learn a lot from that.”

Martin emphasized that not weighing the populations in the RWE studies was a deliberate effort to increase the validity of the findings and increase the value of such studies going forward.

“After applying the trial inclusion/exclusion criteria to the best of our ability using the real word data sources that we have, we are intentionally not weighting the population, because going forward in the future, were you to do this without a reference trial, you would have no population to weight your population to,” he said. ☝️

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The rigor of the US Food and Drug Administration's guidance on pregnancy and maternal outcomes studies is illustrated by the difference in postapproval requirements for the two drugs approved for hypoactive sexual desire disorder in premenopausal women, AMAG Pharmaceuticals Inc.'s newly approved Vyleesi (bremelanotide) and Sprout Pharmaceuticals Inc.'s Addyi (flibanserin).

Vyleesi and Addyi have different mechanisms and treatment regimens, but both are approved for the same indication: treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is not due to a co-existing medical or psychiatric condition, problems within the relationship, or the effects of a medication or other drug substance. (Also see "AMAG Must Build Market For Approved Female Libido Drug To Avoid Addyi's Fate" - Pink Sheet, 24 Jun, 2019.)

In the time between Addyi's approval on 8 August 2015 and Vyleesi's clearance on 21 June, FDA drafted new guidances to replace documents on postapproval pregnancy studies and clinical lactation studies from 2002 and 2005, respectively. The new draft guidances, which were both released on 8 April, call for more specificity in study outcomes and a broader range of trial designs to complement traditional pregnancy registries. (Also see "Pregnancy Registries Are Insufficient To Assess Drug Safety, US FDA Says" - Pink Sheet, 8 May, 2019.)

The FDA has been gradually overhauling the vast regulatory framework for identifying and communicating medication risks in pregnant and lactating women and their babies. Such issues were central to the "roadmap" for women's health research launched by the FDA in 2013, and then issued the final version of a major pregnancy and lactation labeling rule (PLLR) in 2014. (Also see "UCB Cimzia Advances Pregnancy And Lactation Labeling For Biologics" - Pink Sheet, 9 Apr, 2018.)

In 2018, the FDA issued a draft guidance on pregnant women in clinical trials that included more opportunities to include pregnant women in the postmarketing setting than in the clinic. (Also see "Pregnant Women In Clinical Trials: US FDA Lays Out Different Considerations For Premarket, Postmarket" - Pink Sheet, 9 Apr, 2018.)

The Vyleesi approval letter illustrates the new environment with a postmarketing requirement (PMR) for a "retrospective cohort study using electronic claims data" that "will complement the postmarketing pregnancy registry." The Vyleesi PMR should compare maternal, fetal/neonatal and infant outcomes in women exposed to Vyleesi during pregnancy against "an internal, unexposed cohort" of pregnant women, who will be matched with Vyleesi-exposed women by age at pregnancy and gestational age at cohort entry.

Both Vyleesi and Addyi were required to establish pregnancy registries. Addyi's PMRs were communicated briefly, among a range of other PMRs and a risk evaluation and mitigation strategy (REMS), with direction from FDA to establish a "pregnancy registry study to evaluate adverse pregnancy outcomes and birth defects in pregnancies exposed to Addyi" and a "maternal-fetal outcome study to evaluate adverse pregnancy outcomes and birth defects in pregnancies exposed to Addyi." The Vyleesi approval letter, almost four years later, requires a "prospective, registry-based, observational cohort study that compares obstetrical, maternal, fetal/neonatal, and infant outcomes in women exposed to Vyleesi during pregnancy to an internal, unexposed cohort of pregnant women."

The Vyleesi letter goes on to specify pregnancy-related outcomes to be identified and adjudicated with medical chart review, including "congenital malformations, spontaneous abortions, elective terminations, small for gestational age [and] pre-term births." The infants should be followed for a year, FDA said.

Until the pregnancy registry is operational, FDA requests quarterly safety reports from AMAG with all postmarketing adverse pregnancy and neonatal outcomes. "If a neonate is determined to have been exposed, assessment of growth and development should be assessed through at least the first year of life," the agency said.

AMAG must also conduct a clinical trial in lactating women who have received Vyleesi "to assess potential adverse effects in the breastfed infant and measure bremelanotide concentrations in breast milk."

"Only a clinical trial (rather than a non-clinical or observational study) will be sufficient," FDA said. The clinical lactation studies draft guidance issued in April noted the paucity of human data on drug use during lactation, and indicated that FDA may require clinical lactation studies more frequently.

**BROADER HORIZONS**

"In the years since FDA issued guidance on this topic, pregnancy safety studies required by FDA have expanded beyond those using data from pregnancy exposure registries (pregnancy registries) to also include other types of epidemiologic studies and pregnancy surveillance," the 8 April draft guidance on postapproval pregnancy studies observed.

The Vyleesi approval letter goes on to specify pregnancy and maternal-fetal outcome studies to evaluate adverse pregnancy outcomes and birth defects in pregnancies exposed to Vyleesi. "The infants should be followed for a year, FDA said.

AMAG must conduct a clinical trial in lactating women who have received Vyleesi "to assess potential adverse effects in the breastfed infant and measure bremelanotide concentrations in breast milk."

"Only a clinical trial (rather than a non-clinical or observational study) will be sufficient," FDA said. The clinical lactation studies draft guidance issued in April noted the paucity of human data on drug use during lactation, and indicated that FDA may require clinical lactation studies more frequently.

**REGULATORY UPDATE**

**US FDA’s Higher Bar For Postmarketing Pregnancy Studies Shown By AMAG’s Vyleesi, Sprout’s Addyi**

BRIDGET SILVERMAN  bridget.silverman@informa.com

Publishing online 26 June 2019
Our major companies have partnered to take blockchain technology used to track food shipments and pilot it for a pharmaceutical tracking system.

The Drug Supply Chain Security Act requires the pharmaceutical industry to have interoperable systems in place by November 2023 among its trading partners to track and trace pharmaceuticals through the supply chain; this provision of the law is generally regarded as one of the toughest to implement. The law is silent on which type of system to use and left this up to industry to decide.

FDA announced the launch of the pilot program in February 2019. (Also see “FDA Announces Launch Of DSCSA Supply Chain Security Pilot Program” - Pink Sheet, 7 Feb, 2019.) In April, the agency announced that Merck & Co. Inc., Walmart, IBM Life Sciences, and KPMG had been selected to pilot the data architecture piece of DSCSA. This is one of 20 pilots operating. Others are exploring the DSCSA governance process and product identifier verification by a contract manufacturing organization.

The pilot will build on the work IBM has already done in building a blockchain program that Walmart is using in tracking food shipments. IBM’s Food Trust network enables Walmart to track foods back to their sources in the event of food-borne illnesses where sources of contamination need to be quickly identified.

**Each Company Brings Expertise To Bear**

The participants said that each company has its own expertise to lend to the pilot.

IBM announced on 13 June that “each company brings unique expertise to the project, which will create a shared permissioned block chain network that allows real-time monitoring of products.”

Merck & Co. told the Pink Sheet that each partner is equally involved and brings expertise to the table, Merck & Co. in supply chain strategy and logistics, IBM with the blockchain technology and experience and Walmart through its participation in a pilot with IBM involving tracking food through the supply chain, and KPMG with integration analytics.

Arun Ghosh, blockchain leader for KPMG, elaborated on the different roles each party will play in the pilot and how the blockchain will work in a recent interview with the Pink Sheet.

He said KPMG’s role is to “help Merck and Walmart and FDA understand the analytical outputs. … We will bring the blockchains to life. IBM will bring to bear their fantastic Food Trust platform … Merck was the visionary, and they will play the end-to-end role.”

**Blockchain’s Anti-Hacking Feature**

Ghosh said that one of the main advantages to a blockchain system is that it is virtually impossible for unapproved users to hack into the system. “It is a very secure ledger system and information stored on it cannot be changed.” This is advantageous in ensuring that the system cannot be hacked by counterfeiters.

Ghosh said that blockchain is a distributed network of computers that share a ledger of information stored in blocks that can only be accessed by participants connected to the network. It is a decentralized system without any central server.

He explained that “each block contains some data and each container has a hash key over it. The hash key is layered over the data. The hash key creates a string of alphanumeric symbols over the data and once created, is almost impossible to reverse engineer or hash back to the original data.”

Ghosh added that “the next block inherits the preceding key and generates a new one. So unless you are in the blockchain, you cannot see anything on the chain or intercept anything. That is the big attraction to a lot of people, especially when you have two or three parties exchange information.”

Under other types of systems, the data can be overwritten, or in the case of encrypted systems, hacked.
He said that with blockchain, once it is written it is written for posterity, as there is no way of getting in and changing anything.

**HOW BLOCKCHAIN WILL WORK**

Gosh explained that a product identifier will be affixed to the drug and this identifier will be used throughout its chain of custody to track its movements through the supply chain.

“The product ID will be created at the time of manufacturing and as the product moves through the supply chain, we will be able to see an immutable ledger from the manufacturing sites to the Walmart pharmacy, so this is the chain of custody of the product. This is a private network so only permissioned users have access to the information.”

Gosh said that the one of the features of the program is a mobile application that KPMG is building. This app will allow the pharmacy to scan the QR code at the time the drug is dispensed. “You will be able see this QR code and you will see this product on the phone when you pick it up.” The QR code is a machine-readable code consisting of an array of black and white squares typically used for storing URLs or other information for reading on a smartphone.

Gosh said that “just like how you track your FedEx package, you will be able to track your products through the blockchain. Through the QR code you will be able to get the whole genus of the product and it will tell you how long it was at the pharmacy before you picked it up.”

Gosh said that during the pilot, only one pharmaceutical product will be tracked. This ensures that “we get the highest fidelity of the system and the most amount of proof. We could go beyond that but it would require a lot of planning.”

The pilot is set to conclude in December.

Walmart VP Karim Bennis said that “with successful block chaining pilots in pork, mangoes and leafy greens that provide enhanced traceability, we are looking forward to the same success and transparency in the biopharmaceutical supply chain.”

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**Lapses In Drug Quality - Marketers Will Also Be Accountable In India**

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India has proposed to make marketers of medicines accountable for the quality of their products alongside the manufacturer.

The proposed rules, notified by the Ministry of Health and Family Welfare, raise the stakes for many large Indian and foreign firms that outsource manufacturing in the country but have not generally been required to partake in manufacturing compliance responsibilities. Currently, under India’s Drugs and Cosmetics Rules, the manufacturer of a drug is responsible for product quality and liable for action in case of deviations.

The ministry notification, dated 24 June, specifies that under the planned rules any marketer who “sells or distributes any drug” will be responsible for “quality of that drug as well as other regulatory compliances” along with the manufacturer. By inference, the rules imply that marketers will be answerable for quality lapses too.

A marketer has been defined under the rules to include a person “who as an agent or in any other capacity adopts any drug made by another manufacturer” for marketing by “labeling or affixing his name on the label of the drug with a view for its sale and distribution.”

The proposed rules, currently open for suggestions or objections, also set out labeling requirements wherein marketers of a drug would need to include their name and address on the label, except if the drug is contained in an ampule or a “similar small container”, in which case only the name of the marketer would suffice.

**CLARITY REQUIRED ON PROCEDURAL ASPECTS?**

The pharmaceutical industry in India, in general, appears to back the new rules, with some experts saying these are long overdue and will help aid quality compliance in the country.

Sudarshan Jain, who recently took charge as the new secretary general of the Indian Pharmaceutical Alliance (IPA), which represents leading domestic firms, said that the group welcomes any move that supports patient safety and quality, but noted that “procedural/implementation aspects” of the new proposed rules are not currently specified.

“The nature of lapses covered, penalties involved etc are not currently clear,” Jain told the Pink Sheet.

The Organization of Pharmaceutical Producers of India (OPPI), which represents foreign firms in the country, was also reported in local media as endorsing the proposed rules, noting it believes that quality should be embedded in every stage of the drug
MANUFACTURING QUALITY

manufacturing process and across the delivery chain — from the R&D laboratory to the pharmacy where the patient buys the drugs.

FIXING THE RESPONSIBILITY OF MARKETERS
Regulations to broaden the scope of responsibility for the quality of drugs in India appear to have been in the making for a while now.

Last year, India’s Drugs Technical Advisory Board (DTAB), a top advisory body to the central and the state governments on technical matters, cleared a proposal to make provisions under the Drugs and Cosmetics Rules to “fix the responsibility” of persons who are marketing drugs without having any manufacturing facility, “using licensed facilities of manufacturers.” (Also see “Third Party Manufacturer Lapses – Marketers Will Need To Share Onus In India” - Pink Sheet, 31 May, 2018.)

The DTAB held at the time that marketing firms should be treated as an “agent of the manufacturer” and no plea under Section 19 of India’s Drugs and Cosmetics Act 1940 should be applicable to it. Section 19 of the Act essentially specifies that no defense in a prosecution can be provided to “prove merely” that an accused was “ignorant” of the nature, substance or quality of the drug or cosmetic in respect of which the offence has been committed, or of the circumstances of its manufacture or import, or that a purchaser, having bought only for the purpose of test or analysis, has not been prejudiced by the sale.

The section, however, provides significant leeway to a person who is not a manufacturer of a drug or cosmetic or is the agent for distribution. Such non-manufacturers are not liable for flouting norms if they prove that the drug or cosmetic had been acquired from a licensed manufacturer, distributor or dealer; or that they did not know and could not, with “reasonable diligence”, have ascertained that the drug or cosmetic in any way contravened the norms; and that the drug or cosmetic, while in their possession, was properly stored and remained in the “same state as when he acquired it.”

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DRUG PRICING

ICER Faces New Foe As Patient, Disability Alliance Takes Aims At Reports On Mayzent, Spravato

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A recently-launched initiative supported by organizations for patients and the disabled called Value Our Health is challenging the value assessments conducted by the Institute for Clinical and Economic Review, starting with ICER’s reports on Novartis AG’s Mayzent for multiple sclerosis and Janssen Pharmaceutical Cos.’s Spravato for treatment-resistant depression.

Value Our Health comprises the Partnership to Improve Patient Care and 37 other advocacy organizations, many of which have relationships with biopharma manufacturers. PIPC members include patient and physician organizations as well as the Pharmaceutical Research and Manufacturers of America and the Biotechnology Innovation Organization.

The initiative responds to ICER’s growing influence among payers in the US, VOH organizers said during a 21 June call with reporters.

One example of that influence is CVS Health Corp.’s announcement in August 2018 that it would rely on ICER assessments to threaten non-coverage for any new drug whose price exceeds a certain cost effectiveness threshold, with the aim of lowering list prices. (Also see “CVS Launching Program To Exclude New Drugs Deemed Not Cost Effective “ - Pink Sheet, 9 Aug, 2018.)

Value Our Health takes issue with ICER’s use of quality-adjusted life years (QALY) as a metric for evaluating cost effectiveness, a practice manufacturers have long criticized as a one-size fits all approach that overlooks the needs of certain patients.

“It is disappointing that ICER continues to reference the QALY as

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the ‘gold standard’ despite that it distorts and misrepresents how patients value their own lives, and it can lead to insurers and the government to deny care to people who would benefit from it,” PIPC executive director Sara van Geertruyden said.

“Value determinations based on QALYs and similar average metrics often fail to acknowledge side effects and differences in effectiveness for populations that are far from average,” added PIPC disability advocate Ari Ne’eman.

“If you are evaluating efficacy of two drugs for same condition, MS or depression, you shouldn’t use QALY as ICER does, you should use measures specifically developed and normed to those certain conditions which would have a much better ability to capture nuance in terms of improvements,” Ne’eman argued.

The organization did not cite a specific method of evaluating cost effectiveness that could replace QALY and acknowledged that none have gained the support to do so in the US so far.

“There are other ways of conducting value assessment, it’s just they just really don’t have the investment that ICER has,”– PIPC’s Geertruyden

ICER received nearly $14m for 2017-2020 from the Laura and John Arnold Foundation to fund its work. That followed a $5m grant from 2015-2017. The organization also receives funding from other sources.

**ICER VALUE FRAMEWORK UPDATE UNDERWAY FOR 2020**

ICER responded to criticism about how its focus on QALY benchmarks could discriminate against vulnerable patient groups or those with disabilities by introducing a complementary metric known as “equal value of life years gained” at the end of 2018.

The metric is “not as flexible as the QALY in capturing benefits to quality of life but does measure any gains in length of life exactly the same across all conditions, regardless of age, severity of illness, or level of disability,” the group explained.

ICER is also in the process of a planned 2020 update to the methods used in its value framework and has solicited public comments to inform the effort. Draft revisions will be released 16 August for further comment.

“We recognize we won’t fully satisfy all stakeholders, particularly those who would prefer a status quo where manufacturers are able to charge any price they’d like for a new drug in this country,” an ICER spokesperson said. “But we’re pleased that ICER continues to play an important role in convening public discussions in the US on how best to align a drug’s price with its benefits for patients.”

**MAYZENT REPORT QUESTIONS COST EFFECTIVENESS**

In the 20 June final report on Mayzent (siponimod), ICER concludes the treatment “does not have a unique role in therapy for any phenotype of MS” and “given its similarities to fingolimod [Novartis’ Gilenya], siponimod should be considered among a group of highly effective disease modifying therapies for relapsing forms of MS.”

The report also noted that “payers may wish to specifically consider granting preferential formulary status to fingolimod when its generic formulation comes to market.”

Mayzent launched at a list price of $88,561 per year, which “exceeds commonly accepted thresholds for cost effectiveness of $50,000-$150,000 per QALY gained, when compared to best supportive care in patients with SPMS [secondary progressive multiple sclerosis],” ICER said.

The analysis focused only on patients with secondary progressive MS, even though Mayzent is approved for the broader indication of relapsing MS. ICER chose to focus on patients with SPMS because that was the population studied in the Phase III trial on the drug, it said.

Novartis took issue with ICER’s approach in a statement. “ICER established the cost-effectiveness of Mayzent based on a comparison to no treatment (best supportive care) while, in practice, most SPMS patients are today treated with drugs that have not been proven in a trial prospectively powered to demonstrate efficacy in a SPMS population,” the company said.

In addition, “Mayzent demonstrated a significant effect in delaying disability progression in a representative SPMS population,” Novartis maintained. “The EXPAND trial was not powered to demonstrate significant differences between groups in the non-active SPMS sub-population.”

**ICER SUGGESTS UP TO 52% DISCOUNT ON SPRAVATO**

ICER’s final report on Spravato (esketamine), also released on 20 June, concludes the drug’s $32,400 annual list price would require a 25%-52% discount to reach a “fair” value-priced benchmark.

Because the drug’s potential patient population is so large, Spravato at $32,400 would have a significant impact on US health care spending, ICER added, triggering an “access and affordability alert” among payers.

“Potentially only 16% of eligible Americans with TRD [treatment resistant depression] could be treated with esketamine per year before crossing ICER’s potential budget threshold of $819m,” the report points out.

Janssen disagreed with the report, maintaining it “underestimates the proven short- and long-term benefits that this treatment, which was granted FDA breakthrough therapy designation, brings to TRD patients in need,” according to a statement.

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Russia Puts The Squeeze On Essential Drug Prices

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A new law came into effect in Russia earlier this month under which originator and generic drug manufacturers must re-register the prices of all their medicines on the country’s essential drugs list and will have to meet tougher requirements with regard to monitoring prices of medicines on the list. The aim of the move is to put downward pressure on the prices of EDL drugs.

Under the 6 June federal law (No 134-FZ), the maximum selling prices of all EDL drugs that were registered before 7 June this year must be re-registered in accordance with a procedure to be approved by the government, according to law firm CMS.

“Manufacturers of reference drugs should ensure that they re-register prices for their medicines in 2019 and 2020,” CMS says, “otherwise they will not be able to sell their drugs on the Russian market.”

Re-registration of prices of generic and biosimilar medicines, by contrast, will happen automatically, without the marketing authorization holder (MAH) having to file a re-registration application with the ministry of health.

“At present, prices that have not been updated for several years and were registered when various rules and techniques were in force are included in the Register of EDL Medicine Prices,” according to CMS. “As a result, drugs are often sold at unreasonably high prices, which reduces the availability of EDL medicines for patients.”

Registrations of price increases are allowed only once a year, and must be implemented before 1 October. There is no such limit for price reductions.

The government will now establish a re-registration procedure and announce when drugs whose prices have not been re-registered will be prohibited from sale.

RE-REGISTRATION CRITERIA

According to the law, MAHs must reduce the registered price of a drug on their own initiative in any of the following circumstances, CMS says:

• The price of a drug in a foreign currency is reduced in the reference state.
• The price of the reference drug decreases.
• The registered price of the first foreign made generic drug exceeds the price of the second generic drug (regardless of where this drug was produced).
• The registered price of the first generic drug produced in a member state of the Eurasian Economic Union exceeds the price of the second generic drug produced in this or another EEU country.

Previously, Russian legislation did not explicitly oblige drug manufacturers to re-register prices on their own initiative, and price reductions were usually carried out by the MAH upon receipt of an order from the Anti-Monopoly Service of Russia (FAS). Now MAHs are obliged to monitor price changes in reference countries themselves and to update their registered prices.

OTHER CHANGES

These latest changes follow amendments made last year to the rules on re-registration of EDL medicines. Under an 8 October 2018 decree, a single selling price is established for each dosage form and pack size of a generic medicine, regardless of the route of administration.

When registering the selling price for a generic, a corresponding coefficient is applied with reference to the registered maximum selling price of the reference drug, and the registered prices of generics may not exceed those of the originator medicine, says the Russian law firm, Brace.

Moreover, for the purposes of re-registering prices upwards, manufacturers in the EEU must submit a calculation of any increase in the cost of raw materials or production costs, data on sales of the medicine, and copies of contracts confirming any increase in the cost of raw materials and energy costs.

Foreign manufacturers must provide copies of invoices for specific medicines and information confirming the manufacturer’s sale prices for the medicines in foreign countries, and copies of customs declarations for the supply of the medicines, according to Brace.

Published online 25 June 2019
US advisory committee endorsed a significant expansion of the population recommended to receive Merck & Co. Inc.’s human papilloma virus vaccine Gardasil 9 but attached an important caveat – vaccination is justified only for high-risk individuals, who likely represent a fraction of this broader group.

The question remains, however, how individuals at high risk of contracting the sexually transmitted virus will be identified.

The Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices on 26 June voted to recommend HPV vaccination with Gardasil 9 (human papillomavirus 9-valent, recombinant) based on shared clinical decision-making for individuals ages 27-45 years of age who are not adequately vaccinated.

The recommendation aligns with the current indication for Gardasil 9, which is approved by the Food and Drug Administration for use in individuals ages nine to 45. Current federal immunization recommendations for the HPV vaccine do not extend to individuals older than 26 years.

While the ACIP recommendation does not call for routine Gardasil 9 vaccination in the 27-45 age group, it would, if finalized by the CDC, open the door to insurance reimbursement when patients in this age cohort decide to get the vaccine after consulting with their health care provider.

**RECENT LABELING EXPANSION**

Current CDC recommendations call for routine vaccination with Gardasil 9 in people 11 or 12 years old, although vaccination can be started as young as age nine.

Catch-up vaccination is recommended for: females through age 26 years; males through age 21 years; and men who have sex with men, transgender persons and persons with certain immunocompromising conditions through 26 years.

There currently are no recommendations for vaccination of adults older than 26 years.

In October, the FDA approved Merck & Co.’s supplemental biologics license application for use of Gardasil 9 in women and men ages 27 to 45 years. (Also see “US FDA Marches Toward Record Novel Approvals With Ionis’ Tegsedi, Leadiant’s Revcovi” – Pink Sheet, 8 Oct, 2018.)

The ACIP was asked to consider two policy issues related to catch-up vaccination recommendations for Gardasil 9: harmonization across genders to all persons through 26 years; and expansion to persons ages 27-45 years consistent with the vaccine’s current indication.

While the former issue garnered the ACIP’s unanimous endorsement, expansion to the 27-45 age group proved far more controversial.

**CLINICAL DECISION-MAKING VS. NO RECOMMENDATION**

The ACIP was not asked whether there should be a universal vaccination recommendation in the 27-45 age group. Rather, the panel was presented with two options:

- Recommend vaccination based on shared clinical decision-making for individuals ages 27-45 years who are not adequately vaccinated; or
- Do not recommend vaccination for adults older than 26 years.

Merck & Co. said that most women 27-45 years old are susceptible to infection by the HPV types covered by Gardasil 9. The vaccine is highly immunogenic in women in this age group and induces HPV antibody responses that are non-inferior to women ages 16-26 years old, Merck said, adding that the vaccine also is generally well tolerated in the older cohort.

However, the ACIP was presented with data suggesting there would be little benefit at the population level of extending the vaccination recommendation through 45 years of age. The number needed to vaccinate to prevent one case of disease would be approximately 40 times higher for adults through age 45 years compared to the current program, CDC representatives said.

The cost effectiveness ratio for the current HPV vaccination program ranged from cost-saving to about $35,000 per quality-adjusted life year gained; cost per QALY gained by vaccination through age 45 exceeded $400,000 in three of five models, with one estimate exceeding $1.4m.

Various health economic analyses also
suggested expansion would not be cost-effective.

The cost effectiveness ratio for the current HPV vaccination program ranged from cost-saving to about $35,000 per quality-adjusted life year gained. However, the cost per QALY gained by vaccination through age 45 exceeded $400,000 in three of five models, with one estimate exceeding $1.4m.

In addition, there is a global shortage of the vaccine because production capacity is not adequate to meet current demand. This demand/supply imbalance is expected to last for the next three to five years, and in some countries introduction of the vaccine and multi-age cohort vaccination have been delayed due to lack of availability.

Although Merck & Co. said no shortage of Gardasil 9 is anticipated in the US even if vaccination recommendations are expanded to the 27-45 age group, there were concerns among some ACIP members that such an expansion might come at the expense of other countries where shortages exist.

**HIGH-RISK INDIVIDUALS MAY BENEFIT ...**

In a 10-4 vote, the panel recommended vaccination in the older age group based on shared clinical decision-making. This recommendation would allow Gardasil 9 vaccination in persons 27-45 years old to be added to the adult immunization schedule, which generally is required for insurance reimbursement.

In a press release on the ACIP recommendation, Merck & Co. noted the Affordable Care Act generally requires coverage for all vaccines administered in accordance with final CDC recommendations.

Those voting in the majority said some individuals in the older age group could benefit from vaccination, such as people who are newly divorced and returning to the dating scene. However, they said that only a minority of people in this age cohort would benefit, and they called on the CDC to issue guidance to help clinicians identify those individuals who are at risk for HPV infection and should receive the vaccine. “I certainly think that a small number of men and women might benefit from this vaccine,” said Peter Szilagyi, professor and vice chair of clinical research in pediatrics at the University of California-Los Angeles. “The challenge is how to identify high-risk individuals.”

The recommendation for vaccination in people ages 27-45 would “send the message that vaccinating at a younger age is not as important as it is and not as effective as it is.” – Milwaukee health department’s Paul Hunter

Szilagyi said he sees two target groups: those who were high risk for HPV when they were younger and continue to be at risk for new infections; and individuals with new sexual partners or whom for behavioral reasons are now at high risk. “I think that latter group is easier to identify. I think shared decision-making is done all the time in the adult world, it’s sort of standard of care now in the adult world,” he said.

“To me the important thing is to try to identify and then perhaps vaccinate the very small number of individuals who would benefit from the vaccine and not vaccinate the vast majority of 27-45 year old women and men.”

David Stephens, director of the division of infectious diseases at Emory University, echoed the need for clear guidance from the CDC on identifying individuals that would most benefit.

“The issue of shared clinical decision-making in this particular case needs to be well defined by the guidance because I think this is an area where there are certain situations where this vaccine could work and could be effective,” he said.

**... BUT SUPPLY ISSUES AND PRIORITIZATION ARE CONCERNS**

Those in the voting minority said it was not clear who is likely to benefit from vaccination, and they worried that expanding the age range could negatively impact global vaccine supply as well as US immunization rates of teenagers and young adults, for whom the vaccine’s utility is highest.

“We didn’t have details on the shared clinical decision-making and to whom would we be suggesting that this vaccine is appropriate, what size of that population of men and women in that large age group would be suggested to consider this vaccine,” said Kelly Moore, an adjunct associate professor in the department of health policy at Vanderbilt University said. “In the absence of any information on the details of what that meant, and in the presence of supply questions, I did not feel comfortable expanding a recommendation to such a huge population.”

Despite Merck & Co’s assurance about Gardasil 9 availability in the US, Moore said she was concerned that expanding the age range for recommended vaccination could create supply issues that distract “from the priority recipients who are in childhood and their teenage years, and I don’t want to do anything to compromise that.”

Paul Hunter, associate medical director for the City of Milwaukee health department, said he worried that the recommendation for shared clinical decision-making would “send the message that vaccinating at a younger age is not as important as it is and not as effective as it is.”

“I think because of that, and because the guidance might not be quite as clear or as effectively communicated by the public sector … the private sector may communicate this in a way that meets their best interests,” Hunter said.

Instead of trying to talk to parents about vaccinating their children against HPV, individual clinicians “may take the easy way out and emphasize giving it to somebody who’s easier to talk to.”

**Published online 27 June 2019**
Recent And Upcoming FDA Advisory Committee Meetings

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