Wow or Yeow?! FDA Outlook for 2022 and Beyond

On January 28th, 2022, Kinexum hosted the annual webinar, Wow or Yeow?! FDA Outlook for 2022 and Beyond, where a panel of regulatory experts commented on recent and imminent developments in FDA regulation of product development, from pleasant surprises (Wow!) to worrisome concerns (Yeow!). Moderator Dr. Alexander "Zan" Fleming, Chairman of Kinexum, alluding to Jules Verne's Around the World in 80 Days, called the roundtable webinar "Around the Major Centers of FDA in 90 minutes."

Editor's Note: This article is written based on the state of knowledge as of January 28, 2022.

2021 Year In Review: CBER and CDER

David Fox of Hogan Lovells and Frank Sasinowski of Hyman Phelps & McNamara provided a summary of Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) Wows and Yeows for 2021. Per the panelists, on the Wow side of the ledger was the fact that Janet Woodcock was still serving as Acting Commissioner of FDA. Additionally, CDER approved 50 novel drugs and biologics. One out of every two were orphan; one out of every three were oncology drugs; and one out of every four received accelerated approval. Seven of the approvals were monoclonal antibodies (while five were turned down). There was GSK's Nucala for chronic rhinitis with nasal polyps and Leo Pharma's Adbry for atopic dermatitis for those who cannot be treated topically; two Lupus approvals, one of which was the monoclonal Saphnelo; at least nine kinase inhibitors were approved, mostly in and around oncology, for example, Kadmon's Rezurock, that targeted the ROCK2 signaling pathway for treating graft-versus-host disease.

Mr. Fox highlighted some approvals under the categories of "glitzy" and "nerdy," an example of the former including Novartis and Alnylam's Leqvio inclisiran to lower LDL cholesterol in certain patients, with twice yearly dosing. Nerdy approvals included Recorlev, Lybalvi, and Cytalux. Recorlev (levoketoconazole) is a single enantiomer of a previously approved racemic mixture, ordinary ketoconazole, that aims to treat Cushing's syndrome. As a result of its difference from the original racemic mixture, Recorlev may be eligible for statutory new chemical entity exclusivity. Alkermes' Lybalvi combines olanzapine with a new molecular entity, samidorphan. Normally olanzapine comes with clinically significant, treatment limiting weight gain; however, samidorphan mitigates the weight gain side effect. Target's Cytalux is a targeted, fluorescing imaging agent that helps surgeons identify tissue during surgery for ovarian cancer.

Notable Wows for 2021 also include 90 first generic approvals and 4 more biosimilar approvals. There are now 33 total biosimilar approvals.

There were 13 CBER approvals, including the first three approvals with Regenerative Medicine Advanced Therapy (RMAT) designations, which were created under the 21st Century Cures Act and signed into law by President Obama in December 2016. These were the Abecma (CAR T therapy), StrataGraft (cell therapy) for burns, and Rethymic (cell therapy) for a thymus condition. There are currently 1100 active INDs for cell therapies, so it is remarkable that two cell therapies made it through the Office of Tissues and Advanced Therapies (OTAT) to receive approval.

A final Wow for 2021 noted by Mr. Fox was FDA's victory in the US Stem Cell case in the 11th Circuit, which allows them to shut down stem cell clinics. It is good enforcement law to have the rogue stem cell

clinics brought under FDA supervision. Unfortunately, a Yeow was FDA losing two significant appellate court decisions, one of which is discussed more later.

Another notable Yeow for 2021 was the resignation of three FDA advisory committee members in protest over the Adulhelm approval, an extremely rare occurrence. Additionally, there were only 11 CDER-led NDA meetings, a low number for the AdCom process. There was a high number of Complete Response Letters, 18 in total for novel drugs and biologics. From March 2020 through September 2021, there were at least 60 applications that had their action dates delayed because the FDA could not find a way to safely conduct inspections. Moreover, a general Yeow is that the 2019 approval of Avexis' Zolgensma for spinal muscular atrophy was the last gene therapy approved, and there are 1200 active INDs for gene therapies.

2021 Year In Review: CDRH

Kelliann Payne of Hogan Lovells and Minnie Baylor-Henry of Baylor-Henry Associates gave their Center for Devices and Radiological Health (CDRH) Wows and Yeows. Among the Wows, in January 2021, FDA issued a guidance on safer technologies program (STeP) to incentivize companies to innovate around safer medical devices. Additionally, Digital Health Technologies for Remote Data Acquisition and Clinical Investigations guidance focused on the use of digital health technology, such as computing platforms, connectivity, software, and so forth, in clinical trials. The belief is that a wider audience will be reached through using a tablet, phone, or home computer for participation in clinical trials for a medical device. However, it remains to be seen whether it will in fact help with enlisting a broader population in device clinical trials. There was also a device guidance on patient engagement in the design and conduct of medical device clinical studies, and principles for selecting, developing, modifying and adapting patient reported outcomes. This guidance takes into account the importance of patient voice in the design of a medical device. Moreover, CDRH has been training reviewers through the experiential learning program, where reviewers get hands-on experience with medical devices. 2021 expanded this program into the digital health space with a focus on innovation.

Looking forward, the Health of Women Program announced the release of its strategic plan in 2022. Hopefully, there will be a focus on the importance of looking at differentiating factors in medical device clinical trials between men and women. While this program is not new, it is receiving greater attention than it has previously.

In December 2021, CDRH issued a guidance on Emergency Use Authorization (EUA) medical devices encouraging companies to begin thinking about registration and how they will apply for a 510(k), PMA or de novo, as appropriate, upon the eventual revocation of EUAs. There were various Wows for 510(k)s, PMAs, de novos, supplements and HDEs that received approval in 2021. One, BioFire COVID test, got a de novo approval, making it the first and currently only COVID test that went from EUA authorization to full marketing authorization. Another, EaseVRx, a virtual reality device for chronic pain treatment, was granted approval by FDA, demonstrating FDA's focusing on devices that treat pain in light of the opioid crisis. Another, HDE, was granted for a patient specific 3D printed total Talus for avascular necrosis of the ankle. A big Wow was the ability to conduct required site inspection during the pandemic. Finally, OrthoSpace got their shoulder implant orthopedic tissue spacer balloon through a de novo, an uncommon pathway in the orthopedic space).

Two big Yeows for CDRH are that seventy-one 510(k) submissions missed performance goals, mostly in the Departments of In-Vitro Diagnostics, Office of Surgical and Infection Control Devices, and Office of

Ophthalmic, Anesthesia, Respiratory, ENT and Dental Devices; and CDRH pre-sub and other Q-sub meetings are being impacted by the pandemic.

2021 Year In Review: CFSAN

Karin Moore of Hyman, Phelps & McNamara provided a summary of Center for Food Safety and Applied Nutrition (CFSAN) Wows from 2021. First, FDA finally issued the sodium final guidance. Voluntary, short-term sodium reduction targets seek to decrease the average sodium intake of adults from 3,400 milligrams to 3,000 milligrams per day over the next two years. However, these targets still do not achieve the level recommended by the Dietary Guidelines for Americans of 2,300 milligrams. The Food Industry has been working to decrease sodium for years now with mixed successes.

Second, in July 2020, FDA announced a new era of food safety. FDA is using predictive analytics (i.e., 21 FORWARD) to help identify where there could be disruptions in food supply due to pandemic related work absences. It uses artificial intelligence to predict which imported foods pose the greatest risk of violations and then better target their import resources. FDA has conducted a record number of foreign supplier verification inspections despite the pandemic.

Third, FDA focused on strengthening of maternal and infant health and nutrition. It has been working on reducing levels of heavy metals in leading baby food brands for years. It had a workshop on bioactives in infant formula and released an action plan called Closer to Zero on its approach moving forward. Fourth, there was increased use of jointly issued warning letters by the FTC and the FDA, which demonstrates that cooperation is going beyond COVID issues and includes multicompany sweeps. Lastly, FDA finally responded to a citizen petition submitted in January of 1998, and revoked the standard of identity for French dressing.

FDA Commissioner, Accelerated Approval, and Impact of Covid-19

Timothy Franson, MD, at Faegre Drinker, stated that most changes in our environment are driven by a crisis rather than data or thoughtful direction (e.g., real world evidence, accelerated approval, and COVID development). He opened the discussion stating that the January 28th morning media questioning whether or not Dr. Robert Califf would be confirmed as FDA Commissioner is a Holy Cow, and if not, that could be a disaster because Dr. Janet Woodcock cannot be renewed as acting commissioner. Kate Rawson of Prevision Policy pointed out that this path to a new commissioner has been unprecedented due to the extended duration of an acting commissioner. The elongated process to a nomination illustrates the lack of a point person in the White House on FDA issues. The White House was content to allow Dr. Woodcock to run the FDA, but not having a confirmed commissioner for so long was an interesting choice given the pandemic. Concerning White House and FDA communications, Grail Sipes, who is the CDER deputy director for regulatory policy, was announced as taking on a new role in the White House Office of Science and Technology, under Eric Lander, which could provide FDA with an advocate in the White House. While Dr. Franson referenced the news questioning Dr. Califf's appointment, Ms. Rawson believes that it is more likely for Dr. Califf to become FDA commissioner than not, despite lack of clarity at this point in time about whether or not he has the votes, and what seemed to be the lack of activist White House support.

On the subject of accelerated approval, Frank Sasinowski stated that if Dr. Califf is confirmed, decisions are going to be made that could result in major changes. Th path to accelerated approval could be enhanced if employing its pathway is made more attractive within FDA. Ms. Rawson added that the vast majority of accelerated approvals are in oncology because the Oncology Center of Excellence has

become incredibly proficient and comfortable with the pathway, and their advisory committees are comfortable using it. In 2021, Rick Pazdur started cracking down on what he called delinquent or dangling accelerated approvals in oncology, where confirmatory trials either hadn't started, were behind schedule or failed to confirm benefit. A huge Wow is that more than a dozen indications last year were removed either following a negative advisory committee review or in response to a threat of one. Oncology regulators are sending a very pointed message that sponsors need to have a workable plan for confirmatory studies at the time of accelerated approval or they are not going to receive it.

Additionally, Dr. Franson stated a major Yeow is that COVID INDs for therapies and vaccines have overwhelmed the FDA review division. He wagers that over 95% will not be completed or result in any public benefit. Ms. Rawson listed the potential issues of "COVID infected" trials as: potential quarantines, clinical study site closures, travel limitations, interruptions to the supply chain, and COVID-19 infection in patients and clinical investigators. There were a couple of recent advisory committees for rare diseases where clinical trials were impacted by COVID. Both Prader-Willi and Alport syndrome failed with pivotal studies impacted by COVID-19 complicating their efficacy analysis. For Prader-Willi, Ms. Rawson said one could argue that the sponsor had enough subjects to show (had to stop early because of enrollment issues due to the pandemic) an effect if there was one. Mr. Sasinowski went into greater detail on the Prader-Willi trial. He explained that they had projected, let us say, 220 subjects to enroll and had to stop at about 180 because of COVID. Before looking at the data, the Sponsors pre-specified a cutoff at March 2020 because routine is essential for children with Prader-Willi and therefore, it is difficult to evaluate children whose routines have been dramatically upended by the pandemic. This cutoff left the trial with maybe 120 subjects. Additionally, there were other factors that contaminated the trail and it lost the effect. Mr. Sasinowski agrees with Ms. Rawson that there are going to be more and more difficult decisions concerning how to cope, manage, and make accommodations for COVID in a scientifically rational way so that research is not lost. While studies are definitely confounded, the goal is to salvage data in a way to advance public health. However, there will eventually be a study application where COVID infected trials is the underlying review issue.

Moreover, Ms. Rawson pointed out that the next commissioner is going to have to oversee a major catch up in inspections due to COVID-19, and this issue will be a huge management challenge for FDA in the next 12 months. In 2021, there were 60 applications that were held up due to an inability to conduct pre-approval inspections. FDA has only been able to complete about half its normal domestic visits and a small fraction of the overseas inspections. The goal is to return, at least in the United States, to a normal cadence of inspections by April 2022. Due to this almost complete inability to conduct overseas inspections in countries like China and India, FDA has been relying on its European partners and remote assessments. FDA does not think remote assessments are more efficient, a replacement for in person visits, and count as inspections.

Transitions from EUA to Full Approvals

As the pandemic transitions into more of an endemic, Kate Rawson noted the increased pressure from stakeholders to use the emergency use authorization (EUA) pathway for non-pandemic applications. For instance, some stakeholders argue that ALS treatments and opioid addiction products are more fatal than COVID-19 and could be deemed public health emergencies. However, this reasoning was quickly dismissed by the FDA, despite continuing conversations on Capitol Hill. Kelliann Payne stated that CDRH has issued a guidance document that outlines a phased approach for products that have been authorized under EUAs. There is a plan and sponsors are starting to look at their data to see if they have

enough to support a full marketing authorization. However, there is no clear timeline in the transition from EUA to full marketing authorization.

Aduhelm

While some individuals disagree with the Aduhelm approval, Frank Sasinowski has a positive spin on the situation. Mr. Sasinowski stated that the accelerated approval pathway had the effect of, after the first approvals, generating more approvals and quickly transforming a death sentence into a chronic disease. The first accelerated approval was for the first drug for multiple sclerosis (MS), and it generated follow up research and activity in MS. This increased interest led to there now being 17 FDA approved drugs for MS. While there have been decades of vigorous research on Alzheimer's disease, Aduhelm is the first Alzheimer's drug to be approved. If history is any indication, approving Aduhelm might have done a lot more good than bad in the Alzheimer's research space. David Fox drew attention to the tradeoff between uncertainty and unmet need. Aduhelm is a policy decision for the community – how much uncertainty are people willing to accept in order to fill an unmet need? How much are people willing to put into the laps of patients, their families, and providers? Accelerated approval was originally titled conditional approval in FDA's draft of the rule and the White House rejected it, so it was rebranded as accelerated approval. What the discussion surrounding Aduhelm is really about is conditional approval, which requires periodic rechecks of the product and creates a schedule for completing the studies on which the approval was conditioned. Mr. Fox's greatest worry with the Aduhelm approval is that FDA will try to overcorrect and tighten up on other products.

Kate Rawson opined that Aduhelm was probably mishandled from the start. The Aduhelm advisory committee didn't understand the accelerated approval pathway. Normally, accelerated approval is used in a narrow patient population. However, Aduhelm is a very broad label, which makes it receiving approval via this pathway a Super Wow. Additionally, she pointed out that most of the criticisms about Aduhelm are with drug pricing, and it was always going to be an expensive drug.

CFSAN

Returning to CFSAN, Karen Moore highlighted two FDA announcements. First, in June 2021, FDA announced their intention to issue draft guidance on the labeling of plant-based milk alternatives (i.e., whether almond milk is milk or not). The guidance will demonstrate where FDA is going with modernization of standards, how aggressive they are going to be with it, and how much they are going to take consumer sentiments and understanding into consideration. Second, in August 2021, FDA reiterated that hemp extract cannot be used in dietary supplements because the term "dietary supplement" excludes ingredients or items that have been approved as a new drug. Interestingly, not a single cannabis-related piece of legislation has landed on the new President's desk for signing. FDA still claims that CBD is illegal and is not going to take steps on CBD until after federal legislation is in place that allows them to do so. Thus, it is unlikely anything related to CBD will come out in 2022.

Orphan Product Watch

David Fox opened the Orphan Product Watch conversation with FDA losing the Catalyst case in the 11th Circuit, which had to do with the scope of orphan exclusivity. It has been the FDA's position, since orphan program regulations were finalized in the early 1990s, that the seven year period of orphan exclusivity is based on the indication received (i.e., proposal of how to treat the disease and patient population) and not the general disease. However, the 11th Circuit effectively negated FDA's longstanding regulation and stated that the statute says it is exclusivity for the disease or condition. This

ruling is a Holy Cow because it essentially says that receiving approval for a particular orphan drug designation grants ownership of that disease for that drug for seven years.

Frank Sasinowski explained that there are two main ways to get drug approval from FDA. The first is through the 1962 Amendment, which FDA interprets to mean two adequate and well-controlled studies that both hit $p < 0.05$, primary endpoint, and pre-specified primary analysis population. Reaching this standard is extremely difficult with orphan diseases and almost never happens. The second is the FDA guidance document on clinical evidence of effectiveness (May 1998) in which FDA says, if you have one highly persuasive statistical test (e.g., one study that had $p <$ e.g. 0.001), then maybe that can count it as two studies. The endpoint should be something where it is unethical to run a replicate second study. In 1997, a third path to approval provided an alternate solution. The FDA Modernization Act (FDAMA 115) stated that only one adequate well-controlled study with confirmatory evidence is required for approval. This pathway was not very popular. However, in December 2019, a guidance came out and the FDA gave examples of how to achieve approval—one study with a normal $p < 0.05$ and confirmatory evidence, which could be e.g. mechanistic information or an animal model study. In roughly May or June 2021, people started utilizing this pathway because it is much more achievable for rare diseases. In September 2021, FDA approved the drug, LIVMARLI, for a liver disease. The LIVMARLI approval via this path is a huge Wow because it could transform the field of developing therapies for those afflicted with rare conditions, though he noted that nothing in the 2019 guidance restricted this approach only to rare diseases.

CDRH

Returning to CDRH, Kelliann Payne, Minnie Baylor-Henry, and David Fox elaborated further on current developments within the division. Ms. Payne stated that there are increased CDRH discussions and negotiations for machine-learning AI and digital health products to develop what are called "predetermined change control plans." FDA is trying to establish special controls, e.g. with the de novo pathway, that allow manufacturers of such devices to make modifications without returning to FDA every time for approval. Mr. Fox exclaimed that while virtual reality for pain and other neurological issues is a huge Wow, there is a lack of standardization across CDRH and CDER. This lack of harmonization and the potential for the individual Centers and the staff within the Centers to go in different directions on these critical therapeutic areas is somewhat concerning. Ms. Payne refocused on the positives of new digital health applications. Digital neurological and cognitive-behavioral therapy place people in virtual settings that allow them to receive therapy at home, which has far reaching applications. She expects there to be lot more de novos in this space and indications in this area. On the Yeow side, Ms. Baylor-Henry mentioned that CDRH missed its MDUFA target date and all of the other UFAs met their target dates. Additionally, negotiations continue in the Center for Devices and the Industry.

Corporate Culture

David Fox, Kate Rawson, and Timothy Franson all commented on the virtual work environment and its implications on the future. Mr. Fox remarked that FDA is unlikely to return soon to an in-person business environment. The next step is most likely for FDA to open the door to more virtual meetings rather than teleconference only. The worry is that this electronic environment is going to be bad in the long run because it creates too much distance for difficult judgment calls to be made. Ms. Rawson added that she believes there will be a hybrid with lower level meetings remaining virtual for convenience and advisory committees meetings starting to return to in-person. Additionally, a lot of new folks are joining FDA because they can work virtually, so forcing in-person might impose a large strain. There are new people

that joined in this virtual environment that have never met their bosses, which is a problem when it comes to training. Mr. Franson closed by stating that the virtual environment ultimately causes a lack of stimulus for collaboration.

For more information, please check out the webinar here!
- Brontë

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