KINEXIONS SPRING 2022 NEWSLETTER

Obesity Pharmacotherapy: New Era, New Opportunities?

The rapid onset of our current obesity epidemic has caught the public health and medical communities somewhat unaware, with a tripling of obesity prevalence since 1975 such that nearly 40% of adults are obese and ~2/3 are overweight. Given the contribution of obesity to a long, well-known list of co-morbidities, the control of excess adiposity is arguably the public health crisis and challenge of our time. Notably, minority populations are disproportionally affected by this epidemic, further exaggerating existing health disparities and increasing the urgency of successful obesity management**.**

While anti-obesity medicines have been used to some extent since the 1930s, they have not been embraced by the medical community until recently, and only with reluctance in some quarters. This is in large part due to reticence to consider obesity a 'real disease', coupled with stigmatizing those affected with a tinge of moral failure (aka fat-shaming). This tendency to attribute obesity to a simple lack of self-control is sharply contrasted with an eagerness to treat other diseases of lifestyle, such as hypertension and type 2 diabetes, which are often equally treatable with lifestyle modification but do not carry the visible "badge of shame" that characterizes excess adiposity. As an aside, in addition to the well-known changes in our food supply and built environment as well as sleep/circadian disruption and stress that are broadly understood to contribute to obesity, there have also been significant changes to our chemical environment that are not modifiable by individuals; indeed, even wild animals that live adjacent to human communities and highly inbred laboratory mice on highly standardized diets have exhibited a small but measurable increase in adiposity that cannot be attributed to lifestyle.

It's worthwhile to take a quick walk through how we got to our current position in pharmacological management of obesity. Anti-obesity medicines had a rather ignoble start in 1920s and 1930s with the use dinitrophenol (DNP) and its mechanistically predictable side effect of hyperthermia, and the early introduction of amphetamines for weight management in the same era, which then progressed to complex amphetamine-based regimens in the ensuing decades that, while not widely adopted, carried significant risk. Use of, and interest in, anti-obesity therapeutics remained quite limited until two approved drugs of limited utility, the noradrenergic drug phentermine and the serotonergic drug fenfluramine, were found to produce and sustain meaningful weight loss (~10%) when combined in the so called "Fen-Phen" combination in the 1990s. Dexfenfluramine subsequently received approval in 1996, although with lower efficacy than the Fen-Phen combination. Both fenfluramine and dexfenfluramine were withdrawn in 1997 following demonstration of valvular heart disease and of pulmonary hypertension. While phentermine remains on the market, it has limited utility as monotherapy, although does have some utility in combination. Nonetheless, the Fen-Phen combination created a set of expectations of what is achievable with obesity pharmacotherapy; until recently subsequently approved drugs (e.g., Orlistat, Sibutramine, Lorcaserin, Phentermine/Topirimate, Naltrexone/Bupropion) met the efficacy standard for approval, but fell far short of the expectations set by the Fen-Phen consumer experience and were accompanied by significant off-target effects. Two of these (sibutramine and lorcaserin) are no longer on the market for safety reasons.

Largely for these reasons (low efficacy, significant off-target effects leading to poor tolerance, significant safety concerns) the obesity market has until recently been static. With only ~4% of the addressable market treated, obesity represents a substantial unmet medical need and market opportunity. The recent success of GLP-1 agonists in producing more robust weight loss, as discussed below, has clearly signaled strong appetite for a well-tolerated anti-obesity medication with good efficacy, although limited insurance coverage for obesity continues to be a challenge.

Although the GLP-1 agonist liraglutide was approved for treating adult obesity in 2014 and adolescent obesity in 2020, the relatively modest weight loss (~8%) produced was not sufficient to spur substantial uptake. However, the next generation GLP-1 agonist semaglutide produces nearly twice the weight loss (15%) while maintaining a favorable safety and tolerability profile (the typical GI effects that characterize GLP-1 class are generally mild and do not appear to be a major impediment to adoption) such that semaglutide now sets the benchmark for development of anti-obesity medicines. Other GLP-1 agonists and especially incretin-based polyagonists are in development, with several in phases 2 and 3. The most promising approaches to date are polyagonists that target GLP-1 and GIP, such as tirzepatide, those that target GLP-1 and glucagon receptor, and tri-agonists targeting GLP-1, GIP and glucagon receptors. Some, such as tirzepatide, show greater weight loss than semaglutide although they may have greater GI tolerability concerns. Amylin agonists, such as the long-acting amylin analogue cagrilintide, are earlier stage but produce reasonable (~10%) weight loss as monotherapy and impressive weight loss in combination with semaglutide. While these are the most advanced stage therapies, as their development for obesity emerged from diabetes therapeutics, other promising drugs targeting both hunger/satiety pathways and peripheral energy metabolism are in earlier stages of development; these include leptin sensitizers, mitochondrial uncouplers (BAM 15), GDF15 agonists, and PYY agonists. Even with the current and anticipated availability of improved incretin-based anti-obesity therapies, there is ample room and need for these additional therapeutic modalities, especially in light of the heterogeneity of response to any single obesity therapeutic and the incidence of GI intolerance (although predominantly mild) with incretin therapies.

As with any therapeutic indication, translating nonclinical discovery and pharmacology data to clinical efficacy carries significant risk. The good news here, though, is that there is a high degree of correlation between efficacy in the diet-induced mouse model of obesity and subsequent clinical efficacy. The predictive value of these models is strong, but is unfortunately primarily qualitative for a variety of reasons. Firstly, drugs that affect hunger and satiety pathways in mice produce a homogenous response in these highly inbred models, while the clinical response is decidedly heterogeneous. This is, in part, due to the fact that targeting homeostatic eating (hunger and satiety) is more straightforward to model than targeting predominantly hedonic eating patterns that “overrule” homeostatic control. Secondly, significant reductions in food intake in mice has a larger impact on body weight over the relatively short term that these studies are conducted than is generally seen with food intake reductions in humans. Finally, targeting energy expenditure, while qualitatively similar between rodents and humans, is quantitatively different. For example, a drug targeting metabolic uncoupling has the potential to exert a greater effect in mice simply due to the larger relative quantity of brown adipose tissue, as well as the higher metabolic rate per unit mass in mice. While this argues for caution in continuing development of a drug with modest nonclinical effects, mitigating factors include uncertainty surrounding quantitative translational prediction and the opportunity to develop combination products. In short, a negative result in these models is predictive of clinical failure, but a modest result may not be.

Those developing obesity therapeutics should consider early exploration of broader metabolic disease application in light of overlapping mechanisms of action. Semaglutide is a great example here – first developed and approved for diabetes, then for obesity, and now in phase 3 for NASH. Those advancing new obesity medicines would do well to consider broader metabolic indications with high fidelity nonclinical models, recognizing that each indication may require a different dose range. Once in clinic, in addition to early assessment of type 2 diabetes measures as secondary outcomes, exploratory noninvasive NASH biomarkers should be considered as early as possible – certainly in a phase 2a trial, but conceivably as exploratory outcomes in phase 1.

With >95% of obese individuals untreated, the opportunities to develop multiple complementary therapeutics to address this high unmet need is substantial. Heterogeneity of responses to drugs and, indeed, heterogeneity in the underlying causes of the disease, strongly indicate the need for multiple classes of drugs to be used as monotherapy and in as of yet unexplored combinations. The threshold of 10% weight loss considered unattainable a decade ago is now well-surpassed, and we are likely on our way to 20% weight loss and associated opportunity to address a massive burden of medical and psychosocial co-morbidities.

- Michael

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Life and Work in the Evolutionary Pharma Industry

My life before the pharmaceutical industry is mainly connected to Oldenburg, the center of an agricultural region in Northern Germany. During the time of my birth, my parents were living in Wilhelmshaven, the biggest Naval Port in the North. However, the big battleship Tirpitz was still being equipped there and the Britons tried to drop some explosives quite early in the war. My parents thus felt that Oldenburg was a safer place for being borne. Later in the war, around the production of the US movie "Memphis Belle," which participated in raids over Wilhelms-haven, ca. March 1943, my mother moved with her two kids to Oldenburg. I attended regular schools there after the war, developed my interest in photography, construction of radios and amplifiers, and my favorite school topics like French, physics and chemistry. My studies in chemistry, physics, physiochemistry and microbiology were held in Goettingen. Inevitably, I developed skills in handling most of the machine tools available in the decent mechanical workshop of the organic chemical laboratory, where I could construct two model ships (5-mast-full-rigger Preussen and a Spanish galleon) and some equipment for close-up photography with my Leica.

My life in the pharmaceutical industry began in early 1967. Since Bayer (at that time still called "Farbenfabriken Bayer AG") was in the process of completing a brand new Chemical Laboratory for their Pharmaceutical Branch, I was hired and given permission to stay another 6 months at U. Goetingen in order to complete some synthetic work following my earlier work in the synthesis of cyclohexapeptides, the topic of my thesis completed early 1967. Peptides in general did not play an important role as active ingredients of drugs at the time, but there was optimism that this could change in the not too distant future. Following the classical peptide synthesis of the nonapeptide oxytocin by Vicent du Vigneau (Noble Prize 1955), the '60s saw two important events in peptide chemistry:

1. The ingenious method of Solid Phase Peptide Synthesis (SPPS) developed by Bruce Merri-field in 1963 (Nobel Prize 1984), first applied in the synthesis of a tetrapeptide. This method was used to synthesize the nonapeptide bradykinin within 8 days and was used to synthesize the octapeptide angiotensin II in 1965. It has since become the standard method for peptide synthesis, in particular if the alternative of bacterial expression is less favorable.

2. The competitive race of three teams of chemists for the synthesis of insulin, which was successful for the team of Helmut Zahn at RWTH Aachen in 1963.

My work in the new Chemical Lab of Bayer began in September 1967. I joined several groups of chemists, pharmacologists, etc. involved in different discovery programs for interesting small molecules of potential use as drugs for different diseases. One of the programs was targeting molecules reducing the adhesion of blood platelets. A large number of molecules were synthesized and screened for activity in a series of in-vitro and in-vivo models comprising blood platelets and other targets. Researchers were encouraged to provide input in terms of drug candidates into the priority programs, as well as to spend some time on areas of their own imagination and fantasy. My work led to a variety of fatty acid derivates and it turned out that linolic acid derivatives showed promise to be further investigated in human studies. The ethyl ester was chosen as a candidate for a Phase I study in healthy volunteers and a liquid emulsion was prepared by Pharmaceutical Technology. From the regulatory point of view, no special requirements were applicable in Germany at the time: Formal guidelines concerning pharmacotoxicological studies required in the development of drugs before clinical studies and registration were only introduced in 1971 and furthermore linolic acid was regarded as a general component of human food and the corresponding ethyl ester could be regarded as comparable to the

glycerol ester which is the prevailing type of molecule in fatty food.

The study was prepared, but it wasn't carried out. Management had realized that aspirin (ASA), first synthesized in exactly the same company in the year 1888 and found some years before to reduce the aggregation of blood platelets, would be superior to any new drug still to be developed for this indication. There was little to argue against, and the research program was terminated.

I continued my work in the other areas relevant at the time. My extra interest outside of the re-search programs was in new synthetic methods like electro-chemistry and photo-chemistry. Nothing spectacular resulted from these excursions into new methods and from regular re-search work on new active drug candidates.

New Horizons.

In the end of 1970, I was asked whether I would be interested in joining the tiny emerging group of project management being introduced at the time. It had started with the design of a carefully structured development network plan with a few organizational adjustments regarded as appropriate to develop new drug candidates from preclinical to clinical Phases I, IIA, IIB, III, regulatory submission, approval and launch. This structuring of drug development had taken place in parallel to the late stages of development of the New Drug Law in Germany that was finalized in 1974. On the EU level, comparable work had resulted in a 1965 guideline out-lining the essentials of prerequisites (safety, efficacy and quality) for the approval of new drugs replacing mere registration without substantial review.

I agreed to joining this group led by a charismatic boss. In January 1971, I started working on a few new projects in different stages of preclinical or clinical development. Any involvement in project team meetings and regulatory support required for these projects (e.g., INDs and other clinical trials permissions, as well as master dossiers for regulatory submissions) was to be provided by this small group. We also had to provide status reports, keep the network plans (partly with the help of mainframe computers that turned out to be of questionable benefit) and project data files up-to-date, prepare decisions, organize supplies, follow up due dates and chair project team meetings. It turned out that certain countries, mostly those involved in early clinical development or complementary CMC work (like Japan), did require additional support and communication. Following Phase I, the project team chair moved to a representative of the Medical Department.

Marketed products were mainly handled by project teams chaired by marketing managers and in case of regulatory support needed (e.g., change management and labeling), the Regulatory Affairs Department was in charge, a group that formed the complementary part of the Project Management unit within Development.

Important projects in clinical development at the time were nifedipine and clotrimazole. The latter had been a promising candidate for the treatment of systemic fungal infections before I joined Bayer in 1967. It turned out, however, that the efficacy of the compound was fading away due to significant enzyme induction during oral administration. Consequently, the focus of development moved to formulations for topical use, i.e., cream, dermal solutions and vaginal tablets.

Clinical trials with clotrimazole were carried out in a few countries, in particular in Germany, Japan, the US and selected countries with dermal infections not so common in moderate cli-mates. The US was a

very special case since Bayer was a nobody there. The company had lost its assets including the Bayer Cross and trademarks during the first World War and they could be reclaimed only in 1994. Bayer Aspirin was the property of Sterling Drug/Sterling Winthrop. During that entire time span, Bayer was cautious not to use any of its broadly used trademarks “Bayxyz” in the US in order to avoid legal conflicts. Furthermore, it turned out that several at-tempts to develop new drugs in the US failed before the development of clotrimazole (by the Bayer/Schering (Plough) joint venture Delbay), which was approved in the US in March 1975.

The FDA boasted about the short review time of just 9 months, while the average for NMEs at the time was 36 months. The launch (TM Lotrimin) of the cream was slightly delayed because spermaceti (a product from a protected species) had been used and this required re-formulation (all countries) with an artificial excipient of comparable properties.

The regulatory review process in Germany was far more time consuming. Due to interferences with the lengthy emerging of the new drug law, it took almost 30 months before solution and cream were approved in August 1973. Nevertheless, the launch in November 1973 was perceived as a time mark for a new era of a new product.

The development of nifedipine was far more complicated and time-consuming than clotrimazole. The API, a light-sensitive compound formulated with PEG in a soft-gelatin capsule, was the first dihydropyridine in development and it required some perseverance (initially by the inventors) to overcome the initial resistance and disinterest. The indication to be pursued was angina pectoris, not hypertension. Investigations in the mechanism of action led to the under-standing of calcium channel blockers, which took a while. Nifedipine was Bayer’s main asset within a broad research/development collaboration with the French company Rhône-Poulenc. Despite a positive spirit within that cooperation, things got more difficult when projects advanced closer to the market and each partner thought that its candidates in the pipeline were more valuable than the other partners’ products. Rhône-Poulenc gave up its interest in nifedipine at some time.

My first contribution to the nifedipine capsule project was the US IND. That went quite smoothly, but the following steps in clinical development were more difficult. The US organization did not make much progress in clinical development and we were told that physicians involved did not understand the mode of action and were more interested in beta-blockers. It took a while before the project was offered for license to a major Swiss company. This attempt failed after some time and the project was offered to Pfizer. They carried out some complementary studies and got the drug approved in the end 1981, after 21 months of FDA review. Bayer had retained the right to launch this drug 4 years later.

The most important/successful countries for nifedipine after launch in the second part of the ‘70s were Japan and Germany. Japan used to be a country with certain complementary requirements: repetition of some toxicological studies, as well as CMC/stability studies and clinical development in Japan. The acronym most often heard in this context in the pharmaceutical industry was NTB (non-tariff trade barriers), the mix of requirements designed by Japanese authorities reportedly to keep the foreign competition down. Germany was also complaining about the Japanese import restrictions concerning import of German cars. In 1984, the US started “market-oriented/sector selective (MOSS)” talks in order to overcome the obstacles in four areas, including pharmaceuticals. Success was moderate, but the subsequent International Conference on Harmonisation (ICH) brought significant changes—almost unexpected by critical observers—in drug development in all territories involved. I recall one of the last ICH meetings at San Diego, which began just after election day in November 2000. Even a member of

Bayer's Chinese subsidiary attended. At the time, the contribution to global drug development of the Bayer organization in China was next to nothing. A good reason to reconsider the changes in the last 20+ years.

Nifedipine (Adalat) became a very successful drug. Additional formulations were developed (e.g., a slow release tablet for b.i.d. administration and the once daily formulation of GITS/OROS are still being used as effective and well tolerated treatment of hypertension in a broad range of patients). It is of interest to note that nifedipine drug substance and its methods of manufacture have never been subject to patent protection. This sheds some light on the perception of priority of the drug in the early research stages within the company. The first patents were granted for the soft gelatin capsule and subsequent slow release tablet formulations. I re-call being cross-examined on behalf of Pfizer to defend against claims by a generic company against the soft gelatin patent in 1988 (NYC), which was quite successful.

Since Bayer had a significant line of antiinfectives at the time, mainly penicillins, the two Acyl-ureido-penicillins Mezlocillin and Azlocillin that made it to the markets may be of interest. Both penicillins were broad spectrum, but azlocillin was particularly effective against Pseudomonas. The development in Germany started in 1972/1973 and, unlike earlier projects, they were approved early in 1977 in a fairly short time span of four months; azlocillin even with less than 100 patients. Regulators did like the narrow focus in case of azlocillin. The Dutch Head of Health Authority, who had delayed the approval of nifedipine repeatedly, did encourage the submission and approval of azlocillin. Development in the US was more time-consuming be-cause colleagues in clinical development were hesitant due to the uncertain commercial success and the overlapping process of merging with Miles Laboratories. This changed when the right person came onboard, rolled up his sleeves and started working. The commercial success following approval in 1981 has probably not been outstanding, but the team of colleagues involved in the clinical development had consolidated and gained a lot of experience and cohesion for the next anti-infective: ciprofloxacin.

Ciprofloxacin: The first meeting was called end of October 1981 and it was a priority project right from the beginning. We were ambitious to proceed to Phase I within the shortest possible time span. This required synthesis of the API and the definition of the form to be developed (salts or betain) was still open. I found that the Japanese development of Ofloxacin underway at the same time was using betain (not any water soluble salt) and I found this was a missed opportunity with regard to the simultaneous development of an injectable. It was found that ciprofloxacin hydrochloride monohydrate had adequate properties suitable for the development of tablets and injectable. First priority was assigned to the development of the oral administration and some helpful findings contributed to keeping marketing wishes at a level compatible with the initial setting of priorities: an aqueous solution for oral administration was so bitter that the idea soon disappeared, and an injectable solution for IM administration of 2.5 % was problematic in terms of local tolerance. The initial idea of a 1% solution for IV infusion or injection was soon given up, due to some cloudy solid material appearing in the vials. It was decided to abandon the hydrochloride and to switch to the lactate at a lower concentration, which was made from the betain (code q 3939) and lactic acid.

Following two 4-week studies in rats and dogs, we could proceed to clinical Phase I in May 1982, more or less 6 months after the start. This was possible in Germany since the regulatory requirement at the time was to deposit the nonclinical safety studies (toxicology and pharmacology) and Health insurance details with the Health Authority. No information on study parameters, protocol or CMC was required. The first study compared tolerance and PK of a capsule containing the API and an aqueous oral solution (a somewhat brave part of the study due to the bitter taste). Bioequivalence was shown.

It was common at the time to expand clinical development in more countries when Phase I study results were promising and resources in clinical development could be established. The fact of having jointly developed two penicillins not too long ago was helpful for fast implementation. The development of a Project Target Profile outlining location and bacterial strains responsible for the infections became an important tool in the coordination of targets. Given the daily doses, drug supply became a challenge but never caused a delay in progress. In most countries, the time span between oral development (Tablet) and Injectable was approximately 1.5 years and grew, as in the US, to 3 years with regard to the launch. Ultimately, the injectable was approved there on the basis of bioequivalence.

Regulatory submissions in Germany for tablets and injectable were made in October 1985. At the time the German Health Authority (BGA) was flooded with thousands of submissions referring to the mostly unknown original submissions, a procedure scheduled to end soon after the implementation of a drug amendment. We tried to overcome this blockade and were told that a priority review had been established, due to the efficacy of ciprofloxacin and the fact of hav-ing both the tablet and the injectable solution.

Bayer has undertaken more efforts to develop line extensions of ciprofloxacin which turned out to be quite time-consuming: Cipro oral suspension and Cipro OD. Furthermore, a variety of NMEs were taken into development and one of them, Moxifloxacin, with an increased efficacy against gram-positive and intracellular strains, was launched end of the century. In the mean-time, many earlier chinolones have disappeared and the remaining ones are subject to regulations to ensure that the potential benefit outweighs the risk of their use. Ciprofloxacin and Moxifloxacin which have much contributed to Bayer's success, are still available.

Following my years at Bayer, I was invited to support a start-up project for T1D that was seek-ing advice from Health Authorities in the EU EMA and the US FDA. This project could not be continued after 2006. I was, however, invited to join Dr. Alexander Fleming and his Kinexum team to start an anti-tumor project in Hong Kong and China, and to transfer and convert it into a successful IND in the US. The molecule was a pegylated protein. The issue on the CMC side was that the pegylation pattern of earlier and later protein batches were not really identical and the client had to repeat synthesis/purification of the recombinant protein and its PEG version, as well as repeating some toxicology studies.

This was the first of a long list of projects which followed, including small molecules, peptides, recombinant proteins and broad variety of projects and combinations of very different sources. This work on various scientific topics was always fascinating to me and brought together different people from different races, cultures, colors and religions, and I regard this as a main ingredient of a peaceful world and the enrichment of my life.
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Big Data, Health, Covid-19 and Longevity

On January 19th, 2022, Kitalys Institute held the webinar Knowledge is Power: Realizing Disease Prevention and Individualized Disease Management, in which Stanford's Michael P. Snyder, Ph.D., discussed advances in harnessing Big Data to transform healthcare from population-based medicine to personalized medicine. This webinar was truly fascinating as it examined the huge improvements possible within healthcare that could occur simply from switching from our current model to one in which relevant wellness parameters and values are monitored by wearables and sensors 24/7 in real time

The current healthcare system focuses on treating people after they become sick instead of focusing on intervening earlier to maintain healthy living. Additionally, population measurements determine health decisions rather than individualized data. Dr. Snyder and his lab hope their current research utilizing "-omics" technologies for early disease detection will solve these current healthcare challenges.

Dr. Snyder noted that each person's baseline oral temperature varies slightly, but a few degrees determines whether or not an individual is sick. Thus, if a person feels sick and goes to a doctor's office, the doctor may tell them they are healthy because the doctor compares the patient's current temperature to the population normal spread, and the patient is within these values. However, this person could actually be quite sick because they are much higher than their baseline temperature. While population measurements provide parameters, more personalized measurements assist in providing better treatment.

Dr. Snyder and his lab thus have set up a personal -omics profiling system that follows an individual's epigenome, microbiome, physiology, etc. using various technologies. For the last nine years, they have been running a study collecting data on 110 originally healthy participants, including Dr. Snyder himself. Through collecting multiple data measurements longitudinally, they better track and analyze each participant's health status. The lab takes data when people get sick, go on trips, etc. to see how measurements alter in order to determine what it means to be healthy, how health changes over time, how it differs between people, and what happens when individuals get sick. The goal is to diagnose diseases pre-symptomatically in order to intervene early and maintain health. Individuals are also genome sequenced to see if they possess a potential risk for Mendelian diseases, such as BRCA mutations that indicate a high risk for breast and ovarian cancer in women. By discovering these genomic sequences, individuals are able to better customize medications and take preventative measures.

The Snyder Lab additionally developed a new way of analyzing genomes that is more inclusive than the current Polygenic Risk Score method. For instance, they studied Abdominal Aortic Aneurysm (AAA), a genetically heritable disease, using their analysis method. AAA accounts for 10% of deaths in people who are 60 years or older and diagnosis usually only occurs with the growing and eventual bursting of the aorta. Using whole genome sequencing, machine learning and electronic health record information, they identified 60 genes involved in AAA and a risk score system with 0.8 risk prediction. This approach can apply to other diseases, such as ALS and severe COVID.

The Lab discovered that an individual's personal health profile remains relatively stable throughout life, and a larger difference exists between people than between when the same person is healthy or has an infection, thereby further demonstrating the importance of personalized (over population-based) medicine. Combining different techniques—genome sequencing, imaging, biochemical measurements, biomarkers, metabolites, transcripts, mRNA, clinical labs, cytokines—allows for the detection of a wide array of pre-disease states. The more data collected on a person, the more Dr. Snyder's lab knows what health measures are best for them. Since individuals respond differently to various types of treatments, obtaining these measurements helps a person better take care of themselves and prevent the onset of diseases.

Dr. Snyder explained that most molecules are relatively stable, but some change seasonally (in winter and late spring) and some change through aging. His lab decided to specifically focus on how people's molecules change over time by grouping 43 people into ageotypes (i.e., aging patterns) by kidney, liver, metabolic, and immune agers. Through looking at clinical markers associated with ageotypes, they

discovered not all individuals aged in every category at the same rate. The goal of ageotype research is healthspan extension and morbidity compression. With this mission in mind, Dr. Snyder formed the company, QBio, which conducts deep data profiles, MRIs, and other tests to track people longitudinally and therefore pre-symptomatically catch diseases and cancers, such as ovarian, prostate, and pancreatic.

Given the spread and growing accessibility to wearable digital sensors, Dr. Snyder touched upon his work with wearables, which started eight and half years ago. Wearables serve as a powerful form of technology because 50 million people wear smart watches and these devices can take hundreds of thousands of measurements every day. People track heart rate, heart rate variability, respiration, etc. and can detect material, as well as immaterial, shifts from baseline rates.

In March 2020, when Covid-19 started to lock down normal social activities, the Snyder Lab was working on improving wearable detection algorithms. Pivoting attention to the pandemic, they partnered with wearable technology companies and launched an IRB approved study which immediately enrolled 5,300 people to test a Covid alert system. Comparing trends in the days preceding positive diagnosis with Covid-19, the algorithm predicted Covid in 26 of 32 positive diagnoses a median of four days prior to symptoms and seven days prior to diagnosis based on elevated resting heart rate. They noted however that the alert is not specific for COVID, so other illnesses are picked up as well. Dr. Snyder's lab is working on determining the optimal resolution for different kinds of conditions (i.e., infectious disease, mental stress, etc.). To join a wearables study, see here. The ultimate goal is to make this health detection system available to everyone.

Dr. Synder also discussed his research with continuous glucose monitors on normal and prediabetic individuals. The lab found that not only do prediabetics and diabetics undergo moderate to severe spikes in glucose, but also normal people do too. Therefore, they wrote an algorithm classifying individuals into glucotypes—severe, moderate, and low—based on elevated sugar levels. The results demonstrated people spiking to different foods. With this data, Dr. Snyder started another company, January AI, that shows users their wearable, clinical, and other data on various timescales. Users can then monitor themselves and share data with physicians to improve health diagnosis. This platform builds personalized health profiles using machine learning to determine correlates to beneficial health outcomes for the specific individual. January AI also builds personalized metabolic control systems.

All of these research efforts into harnessing -omics data support Dr. Snyder's ideal world consisting of people getting their genome sequenced before they are born, and then obtaining physiological measurements along with deep biochemical and wearable measurements throughout their lifetimes for more accurate disease risk prediction and early disease detection.

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

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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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