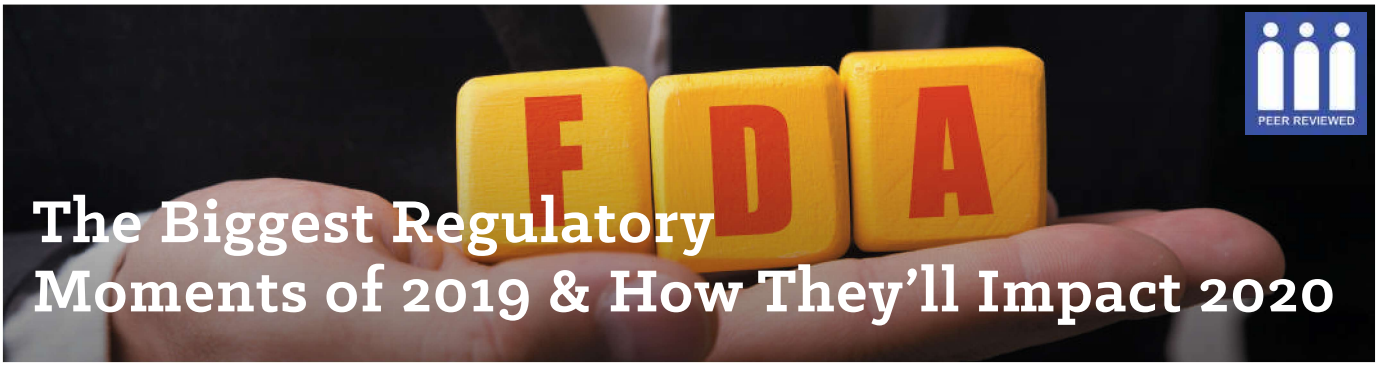

The Biggest Regulatory Moments of 2019 & How They'll Impact 2020

2019 saw many noteworthy changes across the world in the regulatory industry. This article serves to provide the reader with a snapshot of a selection of the changes that have impacted the industry last year and will continue to do so, although it is by no means an exhaustive listing of all the changes globally.

FDA Updates

In the US, following on from a few changes at the FDA that were set in place from Scott Gottlieb's resignation in March last year, Dr. Stephen Hahn was confirmed by the Senate in December. Dr. Hahn has taken over from Dr Brett Giroir, an interim commissioner who took over after the previous acting commissioner, Dr. Ned Sharpless, left. Dr. Hahn's prior position was chief medical executive at the University of Texas MD Anderson Cancer Center.

At the beginning of this year, the FDA published its annual list of "novel" drugs.[1] The list of 48 "novel drugs" includes new drug applications (NDAs), biologic license applications (BLAs) and other incidental categories. 2018's total was 59, however the level of activity is still trending higher than the 10-year average of 36. This demonstrates the positive environment for drug research and development in addition to the uptake of the variety of expedited pathways that FDA have in place. In fact 29 of the 48 drugs (60) had one or more of the expedited review categories (Fast Track, Breakthrough, Priority Review, and/or Accelerated Approval). Twenty-one of them received orphan-drug designation (which gives some added benefits to the drug developer) and 33 of the novel drugs (69%) received their first global approval in the US.

In April 2019, the FDA announced changes in the FDA's Office of New Drugs (OND)[2] that would create enhanced review zones that would intersect disease areas and divisions, to maximise access to more focused and innovative areas of regulatory expertise. The changes increased the number of OND offices overseeing product reviews from six to eight, and increased the number of specific clinical review divisions from 19 to 27. The intent is to provide greater consistency and nimbleness.

OND's Implementation of the Reorganisation

The changes to the structure of OND occur in four phases, as described below.

Phase I: October/November 2019

- The Office of New Drug Policy (ONDP), Office of Program Operations (OPO), Office of Drug Evaluation Sciences (ODES), and the immediate offices of Office of Regulatory Operations (ORO) and Office of Administrative Operations (OAO) will be "stood up".

Phase II: November/December 2019

The Office of Antimicrobial Products (OAP) will become the Office of Infectious Diseases (OID)

- Division of Anti-Infective Products (DAIP) will become the Division of Anti-Infectives (DAI)
- Division of Anti-Viral Products (DAVP) will become the Division of Antivirals (DAV)
- Division of Pharm/Tox For Infectious Diseases (DPT-ID) will be formed from Pharm/Tox personnel currently in the OAP divisions
- A Division of Regulatory Operations for Infectious Diseases (DRO-ID) will be comprised of regulatory staff from the corresponding clinical divisions in this office and will report to ORO

The Office of Hematology and Oncology Products (OHOP) will become the Office of Oncologic Diseases (OOD)

- Division of Oncology Products I & II (DOP I & II) will be split into three divisions (DO I, II, & III)
- Division of Hematology Products (DHP) will be split into Division of Hematologic Malignancies I & II (DHM I & II)
- Division of Hematology Oncology Toxicology (DHOT) will keep the same name in the new Office of Oncologic Diseases (OOD)
- A Division of Regulatory Operations for Oncologic Diseases (DRO-OD) will be comprised of regulatory staff from the corresponding clinical divisions in this office and will report to ORO

The Office of Neuroscience (ON) will be formed from select divisions in the Office of Drug Evaluation I, II

- Division of Neurology Products (DNP) will split into Division of Neurology I & II (DN I & II)
- Division of Psychiatry Products (DPP) will become Division of Psychiatry (DP)
- Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) will become Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
- Division of Pharm/Tox for Neuroscience (DPT-N) will be formed from Pharm/Tox personnel currently in divisions forming ON
- A Division of Regulatory Operations for Neuroscience (DRO-N) will be comprised of regulatory staff from the corresponding clinical divisions in this office and will report to ORO

Phase III: December 2019/January 2020

The Office of Nonprescription Drugs (ONPD) will be formed from the Division of Non-prescription Drug Products in the Office of Drug Evaluation IV

- Division of Non-prescription Drug Products (DNDP) will be split into two divisions (DNPD I and DNPD II)
- A Division of Regulatory Operations for Non-prescription Drugs (DRO-NPD) will be comprised of regulatory staff from the corresponding clinical divisions and will report to ORO
- Non-clinical staff for ONPD will report to the immediate office of ONPD

The Office of Specialty Medicine (OSM) will be formed from divisions in the Office of Antimicrobial Products (OAP), and the Office of Drug Evaluation IV

- Select staff from the Division of Transplant and Ophthalmology Products (DTOP) will transition to the Division of Ophthalmology (DO)
- Division of Medical Imaging Products (DMIP) will become the Division of Medical Imaging and Radiation Medicine (DMIRM)
- The newly created Division of Pharm/Tox of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (DPT-RPURM) will also provide Pharm/Tox support to the Office of Specialty Medicine once ORPURM is stood up in Phase IV. Non-clinical staff will remain with their original supervisors from original divisions until Phase IV.
- A Division of Regulatory Operations for Specialty Medicine (DRO-SM) will be comprised of regulatory staff from the corresponding clinical divisions in this office and will report to ORO

Phase IV: February/March 2020

The Office of Cardiology, Hematology, Endocrinology, & Nephrology (OCHEN) will be formed from divisions in the Office of Drug Evaluation I, II, III, and the Office of Hematology and Oncology Products

- Division of Cardiovascular and Renal Products (DCRP) will become the Division of Cardiology and Nephrology (DCN)
- Division of Non-Malignant Hematology (DNH) will be formed as a new division with personnel from the Division of Hematology Products (DHP)
- Select staff from the Division of Metabolism and Endocrinology Products (DMEP) will become the Division of Diabetes, Lipid, Disorders, and Obesity (DDLO)
- Select staff from the Division of Bone, Reproductive, and Urologic Products (DBRUP) and Division of Metabolism and Endocrinology Products (DMEP) will become the Division of General Endocrinology (DGE)
- Division of Pharm/Tox for Cardiology, Hematology, Endocrinology, and Nephrology (DRO-CHEN) will be formed from Pharm/Tox personnel currently in Divisions forming OCHEN
- A Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology, (DRO-CHEN) will be comprised of regulatory staff from the corresponding clinical divisions in this office and will report to ORO

The Office of Immunology and Inflammation (OII) will be formed from divisions in the Office of Drug Evaluation II, III and the Office of Antimicrobial Products

- Select staff from the Division of Transplant and Ophthalmology Products (DTOP) and the Division of Pulmonary, Allergy, Rheumatology Products (DPARP) will form the Division of Rheumatology and Transplant Medicine (DRTM)
- Select staff from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) will become the Division of Pulmonology, Allergy, and Critical Care (DPACC)
- Select staff from the Division of Gastroenterology and Inborn Errors Products (DGIEP) will form the Division of Gastroenterology (DG) and the Division of Hepatology and Nutrition (DHN)
- Division of Dermatology and Dental Products (DDDP) will become the Division of Dermatology and Dentistry (DDD)
- Division of Pharma/Tox for Immunology and Inflammation (DPT-II) will be formed from Pharm/Tox personnel currently in divisions forming OII
- A Division of Regulatory Operations for Immunology & Inflammation (DRO-II) will be comprised of regulatory staff from the corresponding clinical Divisions in this Office and will report to ORO

The Office of Rare Diseases, Pediatrics, Urologic, & Reproductive Medicine (ORPURM) will be formed from divisions in the Office of Drug Evaluation III, IV

- Division of Pediatrics and Maternal Health (DPMH) will be aligned to ORPURM in the new structure
- Select staff from the Division of Gastroenterology and Inborn Errors Products (DGIEP) will form the Division of Rare Diseases and Medical Genetics (DRDMG)
- Select staff from the Division of Bone, Reproductive, and Urologic Products (DBRUP) focused on Urologic, Obstetric and Gynecologic Products will form the new Division of Urology, Obstetrics, and Gynecology (DUOG)
- Division of Pharm/Tox of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (DPT- RPURM) will be a newly formed division with shared P/T support to OSM
- Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine (DRO-RPURM) will be comprised of regulatory staff from the corresponding clinical divisions in this office and will report to ORO

FDA Guidance Documents

Over the past year, the FDA issued several new draft guidance documents as well as finalising guidance documents that have been in draft. It is important to note that the guidance describes FDA's current thinking on a topic and are to be viewed as recommendations.

Finalised Guidance Documents from the FDA Include but are not Limited to the Following:

Guidance: Considerations for the Inclusion of Adolescent Patients in Adult Oncology Trials[3] was published to facilitate industry with the recommendation of the inclusion of adolescent patients (ages 12 to 17) in relevant adult oncology clinical trials that are disease and target-appropriate, to enable earlier access to investigational and approved drugs for adolescent patients with cancer. The guidance gives appropriate criteria for the inclusion of adolescent patients in adult oncology trials, dosing and pharmacokinetic (PK) evaluations as well as safety and ethical requirements.

Guidance: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products[4] was finalised "to assist industry in developing enrichment strategies that can be used… to demonstrate the effectiveness of drug and biological products. Enrichment is the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population. Although this guidance focuses on enrichment directed at improving the ability of a study to detect a drug's effectiveness, similar strategies can be used in safety assessments."

Guidance: Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry[5] has been finalised to assist sponsors in the clinical development of drugs and biological products for the treatment of amyotrophic lateral sclerosis (ALS). It provides insight into FDA's current thinking regarding the clinical development for drugs to support an indication for the treatment of ALS. This guidance focuses on specific clinical drug development and trial design issues that are unique to the study of ALS.

Guidance: Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry[6] provides guidance "to sponsors and applicants submitting investigational new drug applications (INDs), new drug applications (NDAs), biologics licensing applications (BLAs), or supplemental applications on the appropriate use of adaptive designs for clinical trials to provide evidence of the effectiveness and safety of a drug or biologic". It describes "important principles for designing, conducting, and reporting the results from an adaptive clinical trial" advising "sponsors on the types of information to submit to facilitate FDA evaluation of clinical trials with adaptive designs, including Bayesian adaptive and complex trials that rely on computer simulations for their design".

Guidance: Placebos and Blinding in Randomized Controlled Cancer Clinical Trials for Drug and Biological Products[7] provides recommendations for the use of placebos and blinding in randomised controlled clinical trials in development programmes for drug or biological products to treat haematologic malignancies and oncologic diseases.

Guidance: Adaptive Designs for Clinical Trials of Drugs and Biologic[8] sets out FDA's recommendations on adaptive trial design principles and the information the FDA will review from adaptive studies submitted as part of investigational new drug applications (INDs), new drug applications (NDAs), biologics license applications (BLAs) and supplemental applications. In addition to minor editorial changes, the guidance also clarifies FDA's recommendations for Bayesian adaptive designs and its expectations for the extent of pre-specification required for governing adaptations to studies.

FDA has Issued the Following New Draft Guidance Documents:
Guidance: Cancer Clinical Trial Eligibility Criteria: Minimum Age for Pediatric Patients[9] gives recommendations "regarding minimum age eligibility criteria and addresses specific situations in which the inclusion of children (aged 2–12) and adolescents (aged 12 to 17 years) is appropriate in cancer trials (i.e., based on disease biology and clinical course, molecular target of the investigational drug, and/or its molecular mechanism)".

Guidance: Rare Diseases: Natural History Studies for Drug Development.[10] The focus of this guidance is rare diseases; however, recommendation 22 in the guidance may be applicable to drug development for non-rare diseases. This guidance describes the broad potential uses of a natural history study in all phases of drug development for rare diseases, the strengths and weaknesses of various types of natural history studies, data elements and research plans, and a practical framework for the conduct of a natural history study. This guidance also discusses some considerations for aligning the study design with study objectives and for enhancing the interpretability of study results; patient confidentiality and data protection issues in natural history studies; and potential interactions with FDA related to these studies.

Guidance: Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics[11] is intended to encourage "sponsors and applicants who are using real-world data (RWD) to generate real-world evidence (RWE) as part of a regulatory submission to FDA to provide information on their use of RWE in a simple, uniform format. RWD are data relating to patient health status and/or the delivery of health care that are routinely collected from a variety of sources. RWE is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD".

Guidance: Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs[12] proposes ways to increase patient diversity in clinical trials. Previously the focus has been to promote enrolment practices; however, this guidance has focused on having sponsor companies to include more historically underserved populations in clinical trials such as women, the elderly and minorities.

Guidance: Non-alcoholic Steatohepatitis with Compensated Cirrhosis: Developing Drugs for Treatment[13] provides much welcomed guidance on "the enrollment criteria, trial design, efficacy endpoints, and safety considerations for phase 3 trials." It also identifies "knowledge gaps that represent important challenges in the development of drugs for this indication."

Revised Guidance: Rare Pediatric Disease Priority Review Vouchers[14]. This revised guidance to industry is to clarify the process and reflect changes as a result of the Advancing Hope Act of 2016. The vouchers (potentially lucrative because they are transferable) can be used to reduce the time of an FDA new drug approval review to six months from ten months. Companies have sold them for as much as $350 million and as little as $80.6 million. The revisions include a new definition for rare pediatric disease, to define the pediatric population as from birth through to 18 years. FDA previously considered the pediatric population as from birth to 16 years. The guidance also explains how the rare pediatric disease PRV program shows how the FDA will not be able to designate products for the rare pediatric disease priority review voucher program after September 2020, and the agency cannot award any rare pediatric review vouchers after September 30, 2022.

Guidance: Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products[15] is a guidance, for comment only, providing guidance to sponsors and applicants on "interacting with the FDA on complex innovative trial design (CID) proposals for drugs or biological products. FDA is issuing this guidance to satisfy, in part, a mandate under section 3021 of the 21st Century Cures Act (Cures Act)." The guidance "discusses the use of novel trial designs in the development and regulatory review of drugs and biological products, how sponsors may obtain feedback on technical issues related to modeling and simulation, and the types of quantitative and qualitative information that should be submitted for review."

Qualification Process for Drug Development Tools Guidance for Industry and FDA Staff[16] is a draft guidance explaining its qualification process for drug development tools (DDTs) in line with the 21st Century Cures Act. It provides a detailed overview of the general concepts surrounding the DDT qualification programme, a discussion of each of the three stages of the qualification process and explains how qualified DDTs may be modified or rescinded.

EMA Updates

Early last year EMA published a questions-and-answers (Q&A) document on the preparatory work that European Union authorities were undertaking to prevent medicine shortages due to the United Kingdom's withdrawal from the EU.[17] The EMA also relocated from London to Amsterdam[18] and reported that Brexit Costs EMA Almost €60M in 2019.[19]

In the same manner as the FDA, the EMA is keen to support drug developers and issued a report on the previous year's workshop that was attended by regulators from the EU's national competent authorities, EMA, the FDA and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), as well as industry representatives. The aim of the workshop was "to discuss scientific and regulatory approaches to address quality and manufacturing challenges encountered during the development of medicines under early access… such as the PRIority MEdicines scheme (PRIME)[20] in the European Union and the Breakthrough Therapy designation[21] in the United States". The report contains recommendations from participants on next steps and areas to be further explored by both the EMA and the FDA.[22]

EMA took note of the European Ombudsman recommendations on avoiding bias.[23,24] In addition, EMA issued a Guide on Consistency of Indication Wording[25] on factors reviewers should

consider to ensure the wording of therapeutic indications is consistent across products. "Stakeholders, who rely on this information for their work, have raised concerns that therapeutic indications may be worded inconsistently and can contain varying levels of detail," EMA writes, noting that more consistent and detailed indications can benefit healthcare professionals, health technology assessment (HTA) bodies and payers.

The EMA finalised a Clinical Development Guideline for New Gout Treatments.[26] Within the guideline, EMA provided recommendations for patient selection, safety and efficacy assessments and clinical trial design, in addition to discussing further considerations for studies in elderly, paediatric and renally impaired patients. However, EMA points out that "the study design, inclusion criteria, primary endpoints and trial duration largely depend on the treatment goal and mode of action of the new drug."

The EU's clinical trial regulation was adopted and entered into force in 2014, but its application is contingent on a functional clinical trials information system, which is determined via an independent audit. The European Commission (EC) recently updated guidance[27] on the incoming clinical trials regulation, with new questions and answers (Q&As) on requests for information (RFIs), how assessment reports will be made public and the sponsor's responsibilities regarding changes to a clinical trial that are not substantial modifications but are relevant for supervising the trial.

Regulatory Agency News

- The EMA offered line-by-line comments and edits on the FDA draft guidance on comparative analytical assessments for biosimilars.[28]
- ICH E8(R1) General Considerations for Clinical Studies draft guideline[29] was released for public consultation. The guideline focuses on designing quality into clinical studies, considering the diversity of clinical study designs and data sources used to support regulatory and other health policy decisions.
- The FDA launched the Expanded Access Pilot 'Project Facilitate'. Under Project Facilitate[30], FDA has set up a call

centre to serve as a single point of contact for oncologists to reach out to for assistance with completing and submitting expanded access requests for single patient investigational new drug (IND) applications.

- FDA undertook its first action under a new international collaboration, Project Orbis, with Australia and Canada, designed to provide a framework for concurrent review of cancer therapies, approving treatment for patients with endometrial carcinoma (31), within a couple of months. FDA announced Project Orbis may expand to Singapore and Switzerland.[32]

- Towards the end of the year, the FDA proposed to withdraw four NDAs after the companies failed to submit annual reports.[33]

Summary

2019 proved to be another year of change within the industry. Drug developers are in a dynamic environment with a constant change within the regulatory landscape. We expect further changes in 2020, but also some stability for agencies as they settle into another routine of what is expected of them as regulators and as what they will expect from drug developers.

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