Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Pipeline

FDA review times for new drugs in ophthalmology

After a pharmaceutical or biotechnology firm completes the chemistry, nonclinical and clinical evaluation of a novel therapeutic agent, they compile all of this information into an application for marketing approval. In the U.S., this submission to the Food and Drug Administration (FDA) is called a New Drug Application (NDA) or, for a biologic agent, a Biologic Licensing Application (BLA). As you might imagine, this is an anxious time for all "shareholders" in this process. For the firms, they have typically spent many years and typically tens or hundreds of millions of dollars to this date, and all that stands between the firms and the market is the FDA. For affected patients and their families, other than the relatively small number of them who participated in the pre-approval trials, a large number will now have access to this novel therapy if the product is found to be safe and effective. For the FDA, they have to review a massive amount of data to assess the benefits and risks of the new treatment, as well as the quality of manufacturing for a stable product.

The key U.S. law that gave the FDA regulatory authority to make benefit/risk decisions on NDAs and BLAs was the Kefauver-Harris act of 1962. In the years that followed, the time interval from NDA/BLA submission until FDA approval ranged from 88 days to 10 years for ophthalmology products. In the late 20th century, the U.S. Congress, FDA and firms came up with a solution to consistently provide more rapid reviews. This compromise resulted in enactment of the Prescription Drug User Fee Act (PDUFA) in 1992, which is reauthorized every 5 years. Under PDUFA, firms pay a fee to support additional reviewers at the FDA. FDA in return "promises" to review most of the NDAs/BLAs in 10 months and some designated as priority review, in 6 months. With PUDFA V or new molecular entities (NMEs), an additional 60 days was added to the PDUFA date (for a total of 12 months and 8 months, respectively).

The fee was initially about US$250,000. Under PDUFA VI it is now approximately US$2.9 million. Fee exemptions and waivers are granted for small businesses or for applications for orphan diseases. Applications have PDUFA target completion dates and their timelines for review are contained within the FDA benchmarks. Also note that this is the *time* to review. It does not guarantee approval, and that review may be a negative decision, or a decision requiring additional effort by the firm.

Approximately 20 years ago, one of us (G.D.N.) reviewed ophthalmic NDAs. The review time for NDAs in the early 1990's had a wide range, with a mean of 44 months [1]. The review time came down to 11 months in 1996 after implementation of PDUFA.

Recently (March 2020), the U.S. Government Accountability Office (GAO) reviewed the FDA review times for the Center for Drug Evaluation and Research (CDER) [2]. They reviewed 637 original NDAs submitted for during period of Fiscal Year 2014–2018 (October 1, 2013 to September 30, 2018). They noted that at the time, CDER had 17 reviewing divisions. Ophthalmology products were reviewed in the Division of Transplant and Ophthalmic Products (DTOP). In September 2019, CDER began expanding to 27 reviewing divisions, with ophthalmology products now reviewed in the Division of Ophthalmology within the Office of Specialty Medicine. The GAO noted the features which impact FDA's review times including if the application involves a new molecular entity (NME), if a major amendment was submitted during the review, and whether the NDA received a priority review. They noted the special programs of accelerated approval, breakthrough therapy designation, and fast track designation [3].

Of the divisions, the two Oncology Divisions had the most NDAs (67). DTOP had 26 NDAs. We estimate that at least 75% of the 26 NDAs reviewed in DTOP were ophthalmology. Of the 26 NDAs submitted to DTOP, approximately 85% were standard reviews and 15% were priority reviews. Of the 26 NDAs, approximately 25% were NMEs (Table 1). The average review time for DTOP was approximately 275 days, which was as rapid or faster than most divisions, with the exception of hematology and oncology, with average review times of approximately 250 days. The median was similar to the mean. However, as one might expect, there was a wide range on the minimum and maximum review time. The GAO concluded that FDA met the PDUFA program goals.

As many readers know, in the U.S., the "practice of medicine" allows physicians to prescribe an approved for a given patient for any indication as they see fit (21 U.S. Code § 396). That said, there are *de facto* limitations on this practice – for example, the medication may not be covered by insurance. Also, there may not be adequate information to practice evidence-based medicine. Thus firms frequently conduct additional research in the form of additional clinical trial(s) to gain additional indications.

While there is much written and analyzed about FDA reviews, it is generally about original or initial NDAs. Relatively little attention has been paid to new uses or new indications for already approved drugs. These applications are typically called a supplement if submitted by the same applicant as the initial NDA. These changes to already approved drugs serve as an important source of innovation and lifecycle management for the ophthalmic industry. Note that new dosage forms with the same indication, another source of innovation, are submitted and reviewed as new NDAs.

Thus, in addition to the information on initial NDAs above, we also reviewed the U.S. law and practice for *secondary* or subsequent applications for these additional indications in ophthalmology. These supplements are covered in the PDUFA framework. There are target timelines for review of supplements containing clinical data. The target timeline for priority supplements is 90% within 6 months and for standard supplements is 90% within 10 months. Originally and up until PDUFA VI (FY 2018–2022), supplements were assessed a filing fee, similar to original NDAs or BLAs, although substantially less. Under PDUFA VI, User Fee Assessments for supplements with clinical data (as

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Table 1
Number and proportion of FDA CDER new drug applications: FY 2014–2018.

	Standard				Priority				
	No NME		NME		No NME		NME		
Division	*No MA*	*MA*	*No MA*	*MA*	*No MA*	*MA*	*No MA*	*MA*	Total
Anesthesia	33 (62)	7 (13)	1 (2)	0 (0)	11 (21)	0 (0)	1 (2)	0 (0)	53
Anti-infective	23 (40)	0 (0)	2 (4)	0 (0)	5 (9)	1 (2)	25 (44)	1 (2)	57
Antiviral	23 (38)	1 (2)	5 (8)	1 (2)	25 (44)	0 (0)	1 (4)	0 (0)	60
Bone, reproductive, urologic	15 (58)	0 (0)	3 (12)	1 (4)	1 (4)	0 (0)	2 (6)	1 (3)	26
Cardiovascular and dental	22 (67)	3 (9)	4 (12)	0 (0)	1 (3)	0 (0)	2 (6)	1 (3)	33
Dermatology and Dental	19 (59)	1 (3)	8 (25)	2 (6)	0 (0)	0 (0)	2 (6)	0 (0)	32
Gastrointestinal	14 (36)	5 (13)	6 (15)	0 (0)	1 (3)	1 (3)	4 (10)	8 (21)	39
Hematology	27 (44)	0 (0)	2 (3)	0 (0)	4 (6)	1 (2)	26 (42)	2 (3)	62
Metabolism	31 (58)	5 (9)	12 (23)	2 (4)	1 (2)	0 (0)	1 (2)	1 (2)	53
Neurology	17 (39)	3 (7)	4 (9)	5 (11)	1 (2)	0 (0)	10 (23)	4 (9)	44
Oncology	22 (33)	2 (3)	7 (10)	0 (0)	3 (4)	1 (1)	26 (39)	6 (9)	67
Psychiatry	14 (56)	0 (0)	4 (16)	2 (8)	2 (8)	0 (0)	2 (80)	1 (4)	25
Pulmonary	27 (64)	0 (0)	8 (19)	1 (2)	2 (5)	0 (0)	4 (10)	0 (0)	42
Transplant and ophthalmology	*16 (62)*	*0 (0)*	*3 (12)*	*0 (0)*	*4 (15)*	*0 (0)*	*3 (12)*	*0 (0)*	*26*
Other	11 (61)	4 (22)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	18
Total	314 (49)	35 (5)	69 (1)	13 (2)	53 (8)	4 (1)	122 (19)	27 (4)	637

NME = New Molecular Entity; MA = Major amendment.
Division names are shortened for this table.
Note: Data are from 637 NDAs that FDA's Center for Drug Evaluation and Research (CDER) received from fiscal years 2014 through 2018 and for which FDA completed its initial review by March 31, 2019. We use the term NDA to include NDAs and biologic license applications (BLA) reviewed by CDER [2].

well as establishment fees) are eliminated, and target timelines for supplements, which remain unchanged, are funded through program fees for marketed products [4].

In order to assess review times for supplemental submissions for ophthalmic drugs, we used our internal list of approved ophthalmic drugs, selecting initial NDA/BLA approvals from 2010 to 2020 (approximately 60 drugs). We manually reviewed FDA CDER's database, "Drugs@FDA", evaluating the type of review (Priority or Standard), type of supplement (indication or dosage form change requiring clinical data), and FDA timeline for review. This list was substantiated through review of independent articles and literature. We excluded from this analysis the many label changes that reflect manufacturing, packaging, safety and pediatric supplements. Thus, we aimed to select only those applications which reflected additional efficacy indications. From the FDA website and review of Summary Basis of Approvals, we developed a list of efficacy supplements for ophthalmic products containing the type of review (Priority or Standard), type of supplement (indication or dosage form change requiring clinical data), and FDA timeline for review. This list was substantiated through review of independent articles and literature.

In our review, we found four products with 11 efficacy supplements in the ten-year review period. As shown in Table 2, two products were in retina and two products were in inflammation. With one exception, the review intervals were either 6 or 10 months. The one exception, a product requiring nearly 4 years between submission and approval, reflects FDA's requests for additional data, and the Sponsor's time to obtain and resubmit that data.

There are several limitations to this analysis. First, it was manual, and thus subject to our identifying ophthalmic drugs, and further selecting which among the supplemental approvals met the criteria for an efficacy analysis. For example, one product had 114 supplemental applications in the 11 years since initial approval. Second, unfortunately, it is not possible from publicly available information to ascertain the designation of all supplements (priority versus standard), which would enable relative comparison to the PDUFA user fee goals. Third, the input for this analysis is only approved drugs, and approved supplemental indications. We are not able to see those drugs either not approved, or currently in development. Finally, we use only U.S. data, which is more generally available that other countries.

That said, there are two clear conclusions: There are relatively few second indications approved (11 indications for 4 products), and in general, FDA meets similar review times for supplemental ophthalmic as for initial ophthalmic indications. Further, one can deduce that higher quality submissions result in more rapid review timelines, this thinking does not take into account that the overall timeline to market may have actually been reduced by a conscious decision on the part of the Sponsor to file as soon as possible. In our experience, we suggest frequent communication with the FDA to assure alignment with regulatory expectations by the Sponsor. The Tufts Center for Drug Development has conducted more extensive evaluations of drug development using confidential data over the entire pharmaceutical and biomedical industry. In general, our conclusions and interpretations are similar [5–8].

Thus, in conclusion, for both initial and subsequent approvals in ophthalmology, review intervals for quality submissions for both initial and supplemental indications appear to be consistent with PDUFA guidelines. This is useful in Sponsors' planning for subsequent marketing and availability to patients and physicians.

News from pharmaceutical and medical device companies

Ophthalmic products related to the ocular surface

- Aldeyra reached an agreement with the U.S. FDA to use tear levels of reactive aldehyde species (RASP) as a measure of efficacy in upcoming clinical studies and is planning to start Phase 3 trials in the treatment of dry eye (June 2020).
- Aurinia submitted a New Drug Application (NDA) to the FDA for the systemic use of voclosporin to the treatment of lupus nephritis. Voclosporin, a calcineurin inhibitor, is also being investigated for the topical treatment of dry eye disease (May 2020).
- Kala announced that FDA has accepted for review its NDA resubmission for Eysuvis™, (loteprednol etabonate ophthalmic suspension 0.25%) for the treatment of dry eye disease (May 2020).
- Novartis' Xiidra® (lifitegrast) was not approved for the treatment of dry eye by the European Medicines Agency (June 2020).
- Ocular Therapeutix dosed patients in its Phase 1 clinical trial of OTX-CSI (cyclosporine intracanalicular insert) for the treatment of dry eye disease (May 2020).
- Oyster Point announced results from its ONSET-2 Phase 3 study of its OC-01 (varenicline nasal spray) for the treatment of dry eye disease (May 2020).

Table 2
Review intervals for supplemental efficacy indications for ophthalmic drugs (calendar 2010–2020).

Drug	Category	New indication	Submitted	Approved	Interval
Ranibizumab (Lucentis®)	Retina	Macular edema following retinal vein occlusion	22-Dec-09	22-Jun-10	6
		Diabetic retinopathy in patients with diabetic macular edema	7-Aug-14	6-Feb-15	6
		Myopic choroidal neovascularization	11-Jul-16	5-Jan-17	5.8
		Diabetic retinopathy	18-Oct-16	15-Apr-17	6.3
Afilbercept (Eylea®)	Retina	Macular edema following central vein occlusion	23-Nov-11	21-Sept-12	10
		Diabetic macular edema	18-Oct-13	29-Jul-14	9.3
		Macular edema following retinal vein occlusion	20-Dec-13	6-Oct-14	9.5
		Diabetic retinopathy due to diabetic macular edema	30-Sept-14	25-Mar-15	9.5
		Diabetic retinopathy	13-Jul-18	13-May-19	10
Dexamethasone (Dextenza®)	Inflammation	Addition of post-operative inflammation indication	10-Jan-19	20-Jun-19	6.0
Difluprednate (Durezol®)	Inflammation	Uveitis	24-Dec-08	14-Jun-12	42.3

Review times are calculated from initial submission until approval. These reflect FDA review time, as well as Sponsor response time in answering FDA requests for additional information.

- RegeneRx announced results of its Phase 3 clinical trial in patients with neurotrophic keratopathy (NK) treated with topical RGN-259 (June 2020).

Ophthalmic products not related to the ocular surface

- Aerie reported Phase 2 clinical results for its AR-1105 (Dexamethasone Intravitreal Implant, July 2020).
- Akili Interactive received U.S. FDA permission to market the prescription-only EndeavorRx, the first game-based digital therapeutic device to improve function in children with ADHD (June 2019).
- Allergan/Molecular Partners' abicipar pegol for the treatment of wet age-related macular degeneration was not approved by the FDA (June 2020).
- Iveric started dosing in a second Phase 3 trial of its Zimura® (avacincaptad pegol) for the treatment of geographic atrophy secondary to age-related macular degeneration (July 2020).
- Kubota Vision announced results from a clinical study of myopically-defocused images in the progression of myopia (May 2020).
- Noveome Biotherapeutics announced results from a Phase 2, multicenter, open-label clinical trial of ST266 in patients with persistent corneal epithelial defects (PEDs, June 2020).
- Oculis announced that based upon a meeting with the U.S. FDA, they are pursuing Phase 3 clinical trials for OCS-01 (topical dexamethasone) for the treatment of inflammation and pain following cataract surgery as well as diabetic macular edema (DME, July 2020).
- Osmotica Pharmaceuticals received FDA approval for its Upneeq™ (oxymetazoline hydrochloride ophthalmic solution, 0.1%, RVL-1201) for the treatment of acquired blepharoptosis, or ptosis (July 2020).
- Roche received approval from Japan's Ministry of Health, Labour and Welfare for its Enspryng® (satralizumab) to treat adults and children with neuromyelitis optica spectrum disorder (June 2020). The firm also announced results of its Phase 3 study of the Port Delivery System with ranibizumab for the treatment of neovascular age-related macular degeneration (July 2020).
- Tarsus Pharmaceuticals announced results of two Phase 2 studies of the effects of its topical TP-03 in the treatment of demodex blepharitis (June 2020).
- Viela Bio received FDA approval for its Uplizna® (inebilizumab), a CD19-directed cytolytic antibody given intravenously, for the treatment of neuromyelitis optica spectrum disorder (June 2020).

Gene and cell therapy

- Adverum reported interim data on the first 3 cohorts of patients, and dosed a patient in the 4th cohort of the phase 1 OPTIC trial of intravitreal ADVM-022, a vector capsid for aflibercept (May 2020).
- Applied Genetic Technologies Corporation (AGTC) announced expansion of its ongoing Phase 1/2 clinical study of its gene therapy treatment of X-linked retinitis pigmentosa (XLRP) caused by mutations in the RPGR gene (July 2020).
- Gensight announced clinical data from an early stage clinical trial, PIONEER, of a combination of its gene therapy (GS030, channel rhodopsin) and light stimulation for the treatment of retinitis pigmentosa (July 2020).
- jCyte announced results from its Phase 2b clinical trial of its cell therapy for patients with retinitis pigmentosa (July 2020).
- Ocugen received orphan designation status for its gene therapy (OCU400) for the treatment of RHO mutation-associated retinal degenerative disease (July 2020).

Other news about pharmaceutical and medical device firms

- Alcon received U.S. FDA approval for a switch of their olopatadine hydrochloride ophthalmic solution 0.7% from prescription to over-the-counter (July 2020).
- Moderna started a Phase 3 clinical trial of its mRNA-1273 vaccine for COVID-19 disease (July 2020).
- Ocuphire is merging with Rexahn. The combined company will focus on the advancement of its pipeline of ophthalmic drug candidates (June 2020).
- Santen negotiated an ex-U.S. licensing deal for jCyte's Jcell, a human retinal progenitor cell therapy initially aimed at treating retinitis pigmentosa (May 2020).

Regulatory, government, and other research news

- Clinical trial researchers are considering the impact of the COVID-19 pandemic, including less consistent follow-up visits, reduced movement, or poorer mental or physical health, on statistical analyses. For example, reduced sample size may decrease the power of studies to detect a treatment effect. Also, it may be challenging to select an unbiased method to adjust for missing data. [9].
- CURE ID, a collaboration between the FDA and the National Center for Advancing Translational Sciences (NCATS), part of NIH, is a repository that captures clinical outcomes when drugs are used for new conditions, in new populations, in new doses or in new combinations. CURE ID is being used as a repository for re-purposing existing drugs for novel indications, including management of COVID-19 (June 2020).
- H. Holden Thorpe Ph.D., editor of *Science*, proposed that education alone will not counter the problem of science denial in the population. Rather, he proposes that "… The only way to win this fight is to harness the same sophisticated tools in the name of science that are being used to tear science down" – meaning to use social media to promote science." [10].
- U.S. Food and Drug Administration (FDA):

  - Estimated that 80% of active pharmaceutical ingredients and 40% of drug products (the finished medication as dispensed to the patient) were manufactured overseas, mainly in China and India. With international trade threatened by the global pandemic, there is a growing concern in the U.S. over foreign pharmaceutical manufacturing [11].
  - Issued a draft guidance outlining the agency's current thinking on the development of drugs containing cannabis or cannabis-derived compounds (July 2020).
  - Revoked the Emergency Use Authorization (EUA) of the Chembio Diagnostic's DPP COVID-19 IgM/IgG System, a SARS-CoV-2 antibody test, due to performance concerns with the accuracy of the test.
  - Revoked the EUA that allowed for chloroquine phosphate and hydroxychloroquine sulfate donated to the Strategic National Stockpile to be used to treat certain hospitalized patients with COVID-19. The agency determined that the legal criteria for issuing an EUA are no longer met (June 2020).
- Legislative bills are pending in several states to allow physicians to dispense prescription medications, currently not allowed (June 2020) [12].
- Pharmaceutical company sales representatives, who typically meet with physicians face-to-face, are having to change their communication to alternate methods during the COVID-19 pandemic. As well, the role of these representatives post pandemic may change (May 2020) [13].
- The ACTIV (Accelerating COVID-19 Therapeutic Interventions and Vaccines) collaborative program was formed by the U.S. National Institute of Health, Food and Drug Administration, Centers for Disease Control and Prevention, and Biomedical Advanced Research and Development Authority; other U.S. government departments including the Departments of Defense and Veterans Affairs; the European Medicines Agency; and representatives from academia, philanthropic organizations, more than 15 biopharmaceutical companies, and the Foundation for NIH to develop vaccines for COVID-19 (May 2020) [14].
- The California Institute for Regenerative Medicine (CIRM) is funding a clinical trial and other research related to the COVID-19 program (May 2020).
- The impact of the Best Pharmaceuticals for Children Act (enacted in 2012) continues to be felt. Recent NIH-funded research led to pediatric labeling updates for systemic doxycycline, clindamycin and caffeine citrate (April 2020).
- The National Institutes of Health (NIH):
  - Selected Michael F. Chiang, M.D., as the 3rd director of NIH's National Eye Institute (NEI, July 2020).
  - The NIH Data and Safety Monitoring Board stopped a clinical trial of the safety and effectiveness of hydroxychloroquine for the treatment of adults hospitalized with COVID-19 based upon a judgement that it was unlikely to show efficacy (June 2020).
- The role of the U.S. Centers for Disease Control should be expanded in the COVID-19 pandemic, according to several experts [15–17].
- The University of California announced a transformative open access publishing agreement with Springer Nature (June 2020).
- The US Pharmacopeia (USP) decided against using recombinant Factor C (rFC) from Lonza to replace *Limulus* (horseshoe crab) as a test for endotoxins in pharmaceuticals (May 2020).
- Two key papers on treatment of COVID-19 based upon real word evidence (RWE) were withdrawn due to data issues [18].

Declaration of competing interest

Michelle A. Carpenter, JD consults with numerous pharmaceutical firms. Gary D. Novack PhD consults with numerous pharmaceutical firms.

References

[1] Novack GD. Regulatory review intervals for ophthalmic new drug applications (NDAs) at the U.S. Food and drug administration (FDA). Am J Ophthalmol 1998: 126122–6.
[2] Anonymous. FDA drug approval: application review times largely reflect agency goals. Available at, https://www.gao.gov/products/GAO-20-244. [Accessed 16 May 2020].
[3] Novack GD. Pipeline: the accelerated drug approval. Ocul Surf 2010;8(4):205–7.
[4] Anonymous. PDUFA reauthorization performance goals and procedures: fiscal Years 2018 through 2022. Available at, https://www.fda.gov/media/99140/download. [Accessed 21 May 2020].
[5] DiMasi JA, Chakravarthy R. Competitive development in pharmacologic classes: market entry and the timing of development. Clin Pharmacol Ther 2016;100(6): 754–60.
[6] DiMasi JA. An FDA Report card: wide variance in performance found among agency's dru review division. 2014.
[7] Dimasi JA, Reichert JM, Feldman L, Malins A. Clinical approval success rates for investigational cancer drugs. Clin Pharmacol Ther 2013;94(3):329–35.
[8] Dimasi JA. Innovating by developing new uses of already-approved drugs: trends in the marketing approval of supplemental indications. Clin Therapeut 2013;35(6): 808–18.
[9] Servick K. Pandemic could add noise to clinical trial data. Science 2020;368(6492): 693.
[10] Thorp HH. Persuasive words are not enough. Science 2020;368(6498):1405.
[11] Atlas SW, McCMaster HR. Relying on foreign drugs is dangerous. Wall St J 30 April 2020.
[12] Anonymous. Letting the docs dispense. Wall St J 13 Jun 2020.
[13] Loftus P, Hopkins JS. Drugmakers overhaul the sales pitch amid coronavirus lockdowns. Wall St J 2020.
[14] Corey BL, Mascola JR, Fauci AS, Collins FS. A strategic approach to COVID-19 vaccine R&D. Science 2020;368(6494):948–50.
[15] Horton R. Offline: Why president Trump is wrong about WHO. Lancet 2020;395 (10233):1330.
[16] The Lancet Editors. Reviving the US CDC. Lancet 2020;395(10236):1521.
[17] Gottlieb S. Cut through the fog of coronavirus war. Wall St J 2020. 18 May 2020.
[18] Servick K, Enserink M. The pandemic's first major research scandal erupts. Science 2020;368(6495):1041–2.

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