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Chemistry matters!

In November 2015, Allergan announced submission of a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for a multi-dose, non-preserved (MDNP) version of their cyclosporine ophthalmic emulsion (Restasis®) for the increase of tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. The concern regarding use of preservatives in patients with ocular surface disease is well known to readers of this journal. Since its U.S. approval in 2002, Restasis® has been marketed as a unit-dose, non-preserved product, as has the recently approved lifitegrast (Xiidra®) and many over-the-counter artificial tears and lubricants. While these container/closure systems avoid the issue of preservatives, not all patients like them. For example, a 30-day supply for these twice-daily medications requires 60 foil-wrapped containers, which take up a good deal of space. Also, not every molecule is compatible with an acceptable ophthalmic preservative, and a multi-dose preserved product is not possible. Thus, a MDNP product is of great interest. While there are MDNP ophthalmic products sold in Europe, at the time of this NDA submission, none was approved in the U.S. In the U.S., 21 CFR 200.50 requires that multiple-use products contain a system to prevent contamination [1]. This is typically a preservative, although it could be a system which prevents contamination of the drug product reservoir.

In May 2016, Allergan announced that they received a "complete response letter" from the FDA on this product. Analogous to the previously used term "approvable," [2] it means that FDA is not approving the product pending additional information. In October 2016, presumably based upon additional information submitted by Allergan, the MDNP product was approved.

It is striking to me that in the past year, numerous NDAs for ophthalmic products did not gain approval on their initial NDA submission for reasons related to manufacturing (technically, Chemistry, Manufacturing and Controls [CMC], also known as pharmaceutics). In addition to the Restasis® NDA noted above, this is a matter of public record for five additional NDAs: In July, Ocular Therapeutix's dexamethasone intracanicular implant for inflammation, and Bausch + Lomb's latanoprostene bunod for glaucoma, and in October, Aerie's netarsudil for glaucoma, Nicox's AC-170 for allergic conjunctivitis, and Sun Pharma's swollen nanocellular microemulsion latanoprost for glaucoma. To be fair, in some cases, it was not the product *per se*, but rather apparent problems with Good Manufacturing Practice (GMP) at the manufacturing site [3]. The ophthalmic community may recall that in 2012, the U.S. NDA for another ophthalmic product, Merck's unit-dose non-preserved tafluprost (Zioptan®), was held up for CMC reasons.

There is an upside to the recent FDA review of ophthalmic NDAs. In calendar year 2016, FDA approved a number of drugs for ophthalmology: tetracaine for local anesthesia; bromfenac in Durasite™ for post-operative inflammation (BromSite™); riboflavin and ultraviolet irradiation (corneal cross-linking) for keratoconus and ectasia (Photrexa® Viscous and Photrexa®); adalimumab (Humira®) for the additional indication of posterior uveitis; lifitegrast for dry eye (Xiidria®); atropine sulfate for mydriasis, cycloplegia and penalization in amblyopia; and the above noted MDNP cyclosporine (Restasis®). One of these, lifitegrast, is a "new molecular entity (NME)" by FDA's definition.

If you ask ophthalmic clinicians, I think that most will say that most drugs fail due to lack of clinical efficacy. And indeed, in 2016 and early 2017, several Phase 3 studies for ophthalmic products were unfortunately unsuccessful. Discretion prevents me from explicitly listing them – but while late-stage failures are not desirable from an investment perspective, clinical failures are well recognized. At best, only 32% of large molecules and 13% of small molecules that enter clinical development reach marketing approval [4]. Most of those are for clinical efficacy AND safety reasons. If you ask FDA, they will say most drugs fail for inadequate Phase 2 studies (i.e., determining the optimum dose, and the optimum outcome measure). However, FDA will also say that CMC issues are responsible for a large number of NDA failures as well.

All fields of therapeutics deal with CMC issues – however, ophthalmology is of particular concern, as most products are sterile liquids. Controlling for sterility, stability, and quality in a small, pilot facility for early stage clinical supplies is non-trivial. Even more challenging is full-scale manufacturing of a marketed product. Major capital costs are involved in the design, building, and operation of a sterile manufacturing plant. In addition, a skilled, constantly trained workforce is needed. Providing a sterile air supply and sterile, purified water are just two of the challenges to such an operation. Issues surrounding compounding pharmacies have been known for some time in ophthalmology (e.g., sterility of off-label use of VEGF-Inhibitors) [5]. The seriousness of problems at compounding pharmacies is evidenced by the arrest and trial of an executive of a compounding pharmacy for second-degree murder as a result of 64 patients dying from use of contaminated products [1] (http://www.nytimes.com/aponline/2017/01/06/us/ap-us-meningitis-outbreak.html?_r=0). Most cases of drug shortages are due to CMC issues – i.e., manufacturing of stable, sterile products [6]. CMC issues are also paramount in consideration of generic ophthalmic drugs [7] and using medications in a timely fashion [8]. Medical device applications also require information on physical and mechanical characterization [8] (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/

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PremarketSubmissions/PremarketApprovalPMA/ucm050289.htm). Pharmaceutics scientists with ophthalmic drug development experience are hard to find, and are thus very valuable members of a drug development team. The reasons for the 6 products with CMC issues in 2016 are not clear. It may be that whereas in past years, multiple manufacturing sites were submitted in an NDA, more recently, due to increased costs and complexity, only one site may be qualified. If that one site then has quality issues, the NDA is not approved. It may also be that quality requirements from the FDA, European Medicines Agency (EMA) and International Conference on Harmonisation standards are effectively increasing. Or it may just be serendipity.

Drug discovery starts with an idea about physiology, pathology, and a novel pathway for treatment. Drug development requires integrated efforts in preclinical (pharmacology, pharmacokinetics, and toxicology), CMC (drug substance (i.e., active pharmaceutical ingredient) and drug product (i.e., formulated drug), and clinical areas (efficacy and safety). As well, successful drug development requires good management of these various tasks, an understanding of their interdependencies and timing, and communication with regulatory agencies. Of course, in 2017 in the U.S., it also requires an understanding how novel therapeutics will be reimbursed by payers.

Disclosure

Gary D. Novack PhD consults with numerous pharmaceutical firms.

References

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News from Pharmaceutical and Medical Device Companies

Ophthalmic Products Related to the Ocular Surface

- **IACTA Pharmaceuticals** acquired North American rights to NM133 for the treatment of dry eye, a delivery technology for hydrophobic drugs such as cyclosporine (January 2017).
- **Novaliq** announced results from a Phase 2 results of CyclASol®, a clear, preservative-free cyclosporine A solution, in the treatment of severe dry eye disease (January 2017).
- **Portage Biotech** formed **EyGen**, a new ophthalmic company currently in preclinical development of PPL-003, an anti-inflammatory agent for anterior segment indications (November 2016).
- **Sun Pharma** announced results from a Phase 3 clinical trial of Seciera™ (cyclosporine A, 0.09% ophthalmic solution) for the treatment of dry eye disease (January 2017).

Ophthalmic Products Not Related to the Ocular Surface

- **Acucela** (a subsidiary of Kubota Pharmaceutical Holdings) licensed ocular anti-inflammatory modulators from EyeMedics, which had licensed this technology from the University of Southern California (December 2016). This firm also received orphan designation from theFDA for emixustat hydrochloride for the treatment of Stargardt disease (January 2017).
- **Aerie Pharmaceuticals** announced results from its ROCKET 4 Phase 3 clinical trial of netarsudil in patients with glaucoma and ocular hypertension. The firm withdrew their NDA on this product for chemistry, manufacturing, and control reasons, planning to resubmit in late first quarter 2017. They also completed enrolment in their second Phase 3 trial of a fixed combination of netarsudil and latanoprost, MERCURY 2. They entered into a lease agreement with the Industrial Development Agency (IDA) of Ireland for a new manufacturing plant in Athlone, Ireland (October 2016 through January 2017).
- **Allergan** received FDA clearance for a 510K for its XEN45 *ab interno* implant, a surgical treatment for refractory glaucoma (November 2016).
- **AmorChem** created SemaThera, focusing on a novel therapeutic approach to treat diabetic macular edema (DME) via the Semaphorin 3A (SEMA 3A) target (January 2017).
- **BioTime** is evaluating its OpRegen®, its human embryonic stem cell (hESC)-derived retinal pigmented epithelium in patients with advanced dry form age-related macular degeneration ([AMD], January 2017).
- **Encore Vision**, which is developing a treatment for presbyopia, will be acquired by **Novartis** (December 2016).
- **EyeGate Pharmaceuticals** announced that, following a pre-submission meeting with the FDA, it plans to pursue U.S. regulatory clearance of its EyeGate Ocular Bandage Gel via the De Novo 510(k) pathway (December 2016).
- **Eyenovia** announced Phase 2 results of a micro-formulation of a mydriatic agent in humans (November 2016).
- **ForSight VISION4**, a retinal drug delivery firm, was acquired by Roche Holdings Inc. (January 2017).
- **Genentech** announced results from the Phase III GiACTA study, which evaluated Actemra (tocilizumab) in people with giant cell arteritis (November 2016). They also received FDA approval for Lucentis® (ranibizumab) for the treatment of myopic choroidal neovascularization (January 2017).
- **GenSight** announced results of a Phase 1/2 study of its GS010, a genetic treatment for Leber's hereditary optic neuropathy (December 2016).
- **Hemera Biosciences** isin clinical trials with R59, a complement blocking gene therapy platform as prophylactic treatment for dry AMD and geographic atrophy (January 2017).
- **Inotek** announced results from its MATrX-1 Phase 3 study of trabodenoson for the treatment of glaucoma and ocular hypertension (January 2017).
- **Lin Bioscience** licensed technology from Columbia University for the treatment of “dry” AMD (January 2017).
- **Nemus Bioscience** is in preclinical development of topical NB1111, Δ^9-THC-valine-hemisuccinate, in the treatment of glaucoma (November 2016).
- **Nicox S.A.** is planning clinical studies in 2017 of NCX 4251, its novel ophthalmic suspension of fluticasone propionate nanocrystals, for the topical treatment of acute exacerbation of blepharitis (January 2017).
- **Noveome** initiated a Phase 2 clinical trial of ST266, a complex solution of molecules secreted from proprietary cells, to treat patients with allergic conjunctivitis (December 2016).
- **Ocular Therapeutix** announced results of a phase 3 clinical trial of Dextenza™, an intracanicular dexamethasone drug delivery

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