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

Repurposing medications

As I write this column (November 2020), the world is in the midst of the COVID-19 pandemic. The medical community is using a multi-pronged approach to prevent infections that include efforts to reduce exposures, develop vaccines, and treat infected patients. With respect to prevention and treatment, we hear in our omnipresent news the term "repurposing". This term refers to using medications already approved or developed for other indications [1,2], and "repurposing" them for use in patients with COVID-19 [3–6].

There are several implicit assumptions in the presumed benefits of repurposing – speed, safety and efficacy (or at least "it couldn't hurt"). The adjective most frequently associated with repurposing seems to be "rapid". In my opinion, this assumption is generally correct, if the medication being repurposed is already FDA approved, known to be safe, and if being administered by the same *route* and in a similar or lower *dose* as the approved product. For example, if the approved route and intended COVID-19 route is oral, and the dose no higher than the approved product, then the repurposing is relatively easy. This is a non-trivial issue as evidenced in recent papers. Using the *in vitro* anti-viral potency of ivermectin, Schmith et al. and Al-Kofahi et al. calculated the oral dose for ivermectin that may be required for treatment of respiratory COVID-19 infection [7,8]. That dose is substantially *greater* than the approved dose of ivermectin (200 μg/kg - 60 and 120 mg)[9], thus, the safety of a dose which might be required is unknown. I emphasize that this work is *in vitro* and *in silico* and that at the time of this manuscript, there are no large controlled trials concluding the efficacy of safety of ivermectin in treating COVID-19. For a more current status of ivermectin and other drugs I mention in this article, I direct the reader to the American Society of Hospital Pharmacists "Assessment of Evidence for COVID-19-Related Treatments" at www.ashp.org.

Further, if the approved route is oral, and the intended route is inhalation, there are many issues to solve. Some issues deal with pharmaceutics - e.g., developing a stable drug product formulation. This issue may be non-trivial if the chemical characteristics of the active drug do not lend themselves to a stable aerosol in a physiologically acceptable formulation (e.g., pH, tonicity, etc.) [10]. Even for oral medications "… a common medication error involves improper crushing or dissolving of modified-release formulations, leading to dose dumping. Decreased first-pass metabolism can occur when feeding tubes bypass a portion of the gastrointestinal tract and terminate in the jejunum. In this case, drugs with high first-pass metabolism, such as opioids and beta-blockers, would have increased bioavailability" [11].

The second most frequently used adjective for repurposing is "safety". There is an implicit assumption that the safety of an approved molecule is already proven. That is generally true if the route is the same and the dose is no higher. However, in the case of an oral product being given by inhalation, inhalation safety may be different. The molecule might be intolerable when given directly to the lung. Also, it may be metabolized by the liver when given orally, but not when given by inhalation, and thus the heart may be exposed to a higher level of the parent molecule when given by this route, which may have safety issues. There is the extreme case where people, knowing that *topical* bleach, methanol and ethanol could sanitize surfaces against virus, mistakenly thought it would work internally and consumed the product *orally*, leading to poisonings [12]. Further, the adverse events seen in the population studied for a given indication may NOT generalize to patients with COVID-19. For example, adverse events in the immune system may be more severe in a patient with a compromised immune status.

The third most frequently used adjective for repurposing is "efficacy" – or at least the hope of efficacy – and the implied therapeutics phrase - "it couldn't hurt". In mid-May 2020, Shaffer noted that "… the drugs being tested for repurposing to treat COVID-19 tend to fall into two categories: those that target the viral replication cycle, and those that aim to control the symptoms of the disease." [5] For example, "… the aminoquinolones chloroquine and hydroxychloroquine are polymerase inhibitors classically used as anti-malarial medications." In an article published at that time, Geleris et al. [13] note that these agents "have been suggested as effective treatments for coronavirus disease 2019 (Covid-19) on the grounds of both antiinflammatory and antiviral effects." [14–17] The suggestion about antiviral efficacy for these agents was based primarily upon *in silico* and *in vitro* findings. Clinically demonstrated and approved anti-inflammatory agents (e.g., corticosteroids) may be selected to treat the respiratory inflammation associated with COVID-19 [18]. Immunosuppresion caused by colchicine has also been stated as a reason to try this drug in patients with COVID-19 [19]. I re-iterate the caveat that at the time of this manuscript, there are no large controlled trials concluding the efficacy of safety of these repurposed agents in treating COVID-19 – and that pilot results in a population of patients with severe disease might not translate to patients with milder disease or co-morbid conditions.

Another unintended consequence of use of medications for the treatment of COVID-19 is the impact on supplies for those patients currently using it for more accepted indications.

To date, several approved agents of a variety of drug classes have been tried empirically in patients. The efficacy and safety of some of these treatments has been evaluated in controlled studies. Some have been found no better than a negative control (placebo, vehicle, or standard of care), while others may be hopeful [20–26]. The U.S. Food and Drug Administration (FDA) granted some Emergency Use Authorizations (EUA), and then in some cases retracted it. This situation is continually being updated – however, as of my writing this column, none of these repurposed agents has received marketing approval from the FDA for a COVID-19 indication.

Finally, there is the implication that "it couldn't hurt to try". This concept, previously applied to patients with terminal diseases such as

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end stage cancer, is also called "The Right to Try". It is an intuitive right to use any means possible, however unlikely, to treat patients with "nothing left to lose". However, as described in a column in this journal in 2015, it is not so simple or straightforward [27]. There are certainly legal and financial questions – such as whether state laws passed supersede federal laws that may prohibit some uses, who is legally responsible for negative patient outcomes, and whether insurance firms are obligated to pay for the medications and treatment. However, as expressed by the late Paul S. Lietman, MD, PhD, longtime chief of the Division of Clinical Pharmacology at the Johns Hopkins School of Medicine, it is neither compassionate nor caring to give unproven drugs to a desperate patient. In that article, I conceived of the theoretical situation whereby a new drug did not treat the disease, but just kept a patient from dying, leading to a prolonged, low quality of life. I also theorized that if there is an unknown drug-drug interaction of the new agent with a concomitant medication used to relieve pain that might decrease the efficacy of the latter. This theoretical possibility was raised recently in a review article regarding COVID-19 treatments [11], as well as more specifically for the novel anti-viral remdesivir, especially in patients with comorbid conditions and concomitant medications [28]. I add that remdesivir, which is a new chemical entity, was approved in October 2020, for the treatment of adults and children (12 years and older) hospitalized for COVID-19.

As already noted, this column is likely to be out of date on COVID-19 therapies due to the continuing efforts of the healthcare community at the time of publication. Further, I am certainly not an expert in COVID-19 pharmacology. Rather, I present this as a way to introduce the concept of repurposing for ophthalmic drugs. I presented this topic in this journal in 2009, ("The 'In-between' New Drug Application (NDA))" [29]. In that column, I discussed repurposing under the FDA regulatory term "505(b) (2)". This application differs from a New Chemical Entity (NCE), which is a 505(b) (1) and a generic ("copy product) which is a 505(j). A 505(b) (2) application relies on "… FDA's previous finding of safety and efficacy for the molecule …" Stated differently, there is information outside of the work conducted by the Sponsor that is required for consideration of the marketing application. It may be the chemistry of the molecule (Drug Substance or Active Pharmaceutical Ingredient), the preclinical pharmacology or safety of the molecule or in some cases formulated material (Drug Product), or the clinical safety and efficacy of the molecule or drug product. Note that there are similar regulatory routes in Europe and Asia, although the terminology may differ.

Just like the assumptions about repurposing of drugs for use in COVID-19 in particular, there are a number of assumptions about the 505(b) (2) approach for the more general area of pharmaceuticals. There is the assumption of faster development and safety, as well as less corporate risk with a 505(b) (2) approach compared to a 505(b) (1) approach for an NCE. Of course, there is also less financial benefit for the developing firm – but this is weighed against the above noted decreased risk [30].

In ophthalmology in general, as well as in the treatment of ocular surface diseases in particular, we benefit greatly from the use of drugs first developed for other indications. This includes a wealth of anti-infective and anti-inflammatory agents, the indication for which in ophthalmology is essentially similar to that in systemic medicine. Further, in glaucoma therapy, at least until the 1980's, most agents were first used in systemic medicine. At that time, several ophthalmic pharmaceutical firms decided that ophthalmology was a large enough business opportunity that it was worth developing NCE's primarily for ophthalmology. We then saw the approval of the NCE's dorzolamide, loteprednol etabonate and the prostaglandins (latanoprost, bimatoprost and travoprost). The approval of biologics in ophthalmology, including Vasoactive Endothelial Growth Factor (VEGF) inhibitors is an indication of science for systemic medication (primarily oncology) leading to ophthalmology-specific molecules.

With regard to ocular surface disease, we see a mixture of NCE's and 505(b) (2) approved products. Cyclosporine, approved in several products worldwide, is a molecule first developed for systemic medicine. In publicly available data of approved U.S. cyclosporine products to date, the Sponsor of the new product did NOT conduct basic pharmacology or systemic toxicology studies. Thus, one can assume that they used, by definition, the "505(b) (2)" route. Lifitegrast, approved in the U.S. in 2016 for the ocular surface indication, was an NCE, and thus presumably used the 505(b) (1) route. A formulation of loteprednol etabonate 1% (Inveltys®) for twice-daily treatment of post-operative inflammation and pain following ocular surgery approved by the FDA in 2018 referenced the original approval of this molecule (Lotemax® in 1998 – thus a 505(b) (2)). A different formulation of this molecule was recently approved for the treatment of dry eye (Eyesuvis®, 0.25%, four-times daily), which also used the 505(b) (2) route.

So I return to my initial issue about the assumptions of repurposing – speed, safety and efficacy. Can we make a conclusion regarding these assumptions? There is public information on the timing of the first ophthalmic cyclosporine product in the U.S. – Restasis®. In 1983, it was approved as a systemic agent for the prevention of solid organ graft rejection. In 1997, also for systemic administration, it was approved for rheumatoid arthritis and severe psoriasis. In 1995, this time as a topical agent, it was approved for keratoconjunctivitis sicca in dogs. The Sponsor conducted a Phase 2 study in patients between May 1995 and February 1996 [31]. Phase 3 studies were then conducted, completed as part of their submission of a New Drug Application (NDA) in 1999 (and later published in 2000) [32]. An FDA advisory meeting was held in 1999 and the product was approved in 2003. With regard to the second ophthalmic cyclosporine product in the U.S. (Cequa®), clinical studies were started in 2015 (NCT02254265) [33,34], and the product was approved in 2018. In comparison, lifitegrast was an NCE. Basic research started as early as 2002 [35], and clinical studies started at least as early as 2009 (NCT00882687) [36–39]. The NDA was submitted in 2015, was approved in 2016. With the caveat that it is challenging to pinpoint the start time for development, and that sometimes development is slowed for business reasons, the clinical and regulatory development times for one 505(b) (1) and one 505(b) (2) in the treatment of ocular surface disease (Restasis® vs. Xiidra®) seem similar. Cequa® seemed to be a faster development time than Restasis®; however this is not unexpected.

The 505(b) (2) route is frequently used for drug delivery products which seek to improve the therapeutics of approved products. One recent example in ophthalmology (albeit in glaucoma), is Durysta® (bimatoprost implant), the clinical development started at least as early as 2010 (NCT01157364) [40,41], the NDA presumably referenced the first approved product (Lumigan®, 2001) and was submitted in 2019, and the product was approved by the FDA in 2020. Thus in this case, the 505(b) (2) route was not necessarily a rapid one. This relates, in my opinion, to the challenges of drug delivery for prostaglandins in glaucoma.

Products recently approved and under late stage development in ophthalmology are a mixture of NCE's, "repurposed" medications, biologics, and very specific gene therapy products. As well, there is development of generic medications for off-patent products. This represents the portfolio of business investments across our specialty.

In summary, repurposing is one general development route – but the assumptions of faster, safer and more effective are not universal, and need a case-by-case scientific evaluation.

Declaration of competing interest

Gary D. Novack PhD consults with numerous pharmaceutical firms.

News from pharmaceutical and medical device companies

Ophthalmic products related to the ocular surface

- Aerie Pharmaceuticals announced the commencement of COMET-1, a phase 2b clinical trial of AR-15512 (TRPM8 agonist) ophthalmic

solution for the treatment of patients with dry eye disease (October 2020).
- Kala received U.S. FDA approval for its Eyvsuvis™ (0.25% loteprednol etabonate) for the short-term treatment of dry eye disease (October 2020).
- Neuroptika completed enrollment in a Phase 2 controlled, double-masked clinical trial of NRO-1 for the treatment of patients with dry eye disease (August 2020).
- Ocular Therapeutix commenced dosing in its Phase 2 clinical trial of OTX-CSI (cyclosporine intracanalicular insert) for the treatment of dry eye disease (September 2020).
- Olympic Ophthalmics received FDA de novo request clearance for its iTEAR100, an external prescription device designed to temporarily increase acute tear production in adults by stimulating a cutaneous nerve (June 2020).

Ophthalmic products not related to the ocular surface

- Aerpio Pharmaceuticals announced completion of enrollment in its double-masked, placebo-controlled Phase 2 trial in patients with elevated intraocular pressure (IOP) associated with open angle glaucoma (OAG) or ocular hypertension (OHT). (September 2020).
- Alimera Sciences started enrollment in its NEW DAY clinical trial, a randomized, controlled, multi-center study of its Iluvien® (fluocinolone acetonide intravitreal implant) 0.19 mg as a baseline therapy in patients diagnosed with DME (September 2020).
- Allergan announced results for its Phase 3 GEMINI 1 and 2 clinical trials evaluating the efficacy, safety and tolerability of investigational AGN-190584 (pilocarpine 1.25%) ophthalmic solution for the treatment of symptoms associated with presbyopia (October 2020).
- Apellis announced 18-Month Data from Phase 1b Study of Pegcetacoplan in Patients with Geographic Atrophy (GA, October 2020).
- Aura Biosciences started enrolmment in a phase 2 study evaluating the safety and efficacy of suprachoroidal (SC) administration of AU-011 in patients with choroidal melanoma (September 2020).
- Clearside submitted an IND to the U.S. FDA for its CLS-AX (axitinib injectable suspension) to conduct a phase 1/2a clinical trial in wet age-related macular degeneration (AMD) patients by the end of 2020 (August 2020).
- Kodiak Sciences announced treatment of patients in 3 Phase 3 studies of its KSI-301 for retinal disease (diabetic macular edema (DME) and retinal vein occlusion (RVO, October 2020).
- Kubota Vision received an orphan product clinical trial grant from the U.S. FDA to support the ongoing phase 3 study of emixustat in Stargardt disease (August 2020).
- LumiThera announced a collaboration with Diopsys in a planned clinical study to evaluate the ability of its Photobiomodulation (PBM) treatment using the Valeda Light Delivery System to improve electroretinogram (ERG) outcomes in subjects with dry AMD (September 2020).
- Nicox SA selected a new development candidate, NCX 1728, a nitric oxide (NO)-mediated IOP lowering agents (October 2020).
- Novartis announced results of its Phase 3 KITE study of its brolucizumab vs. aflibercept in patients with DME (Sepember 2020).
- Orasis initiated its NEAR-1 and NEAR-2 Phase 3 clinical studies in the U.S., evaluating its novel eye drop candidate, CSF-1, for the treatment of presbyopia (October 2020).
- Outlook Therapeutics initiation enrollment in its supplemental open-label safety study evaluating ONS-5010/Lytenava (bevacizumab-vikg) for the treatment of wet age-related macular degeneration (AMD, NORSE THREE, October 2020).
- Regenxbio reported data from patients in Cohorts 4 and 5 of the phase 1/2a trial of RGX-314 for the treatment of wet age-related macular degeneration (AMD). They have also activated a phase 2 trial of RGX-314 for the treatment of wet AMD delivered to the suprachoroidal space (AAVIATE, August 2020)
- REGENXBIO started enrollment in its AAVIATE trial, a Phase II trial to evaluate the suprachoroidal delivery of RGX-314 for the treatment of wet AMD (September 2020).
- Roche 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).
- Santen announced that the FDA has accepted for review its NDA for cyclosporine topical ophthalmic emulsion 0.1% to treat pediatric vernal keratoconjunctivitis treatment (October 2020).
- SIFI announced results of a clinical study of its Netildex™ (dexamethasone and netilmicin) gel after cataract surgery (September 2020).
- Trefoil Therapeutics today initiated a clinical trial of its Fibroblast Growth Factor-1, TTHX1114, for the regenerative treatment of people with corneal endothelial dystrophies (CED), including Fuchs Endothelial Corneal Dystrophy (August 2020).

Gene and cell therapy

- 4D Molecular Therapeutics commenced enrollment for a phase 1/2 clinical trial of 4D-125 (AAV gene) for X-linked retinitis pigmentosa (XLRP, August 2020).
- Applied Genetic Technologies Corporation provided additional information about the design for a proposed phase 2/3 trial for its X-linked retinitis pigmentosa (XLRP) clinical program for its gene therapy (Sepetmber 2020).
- Gyroscope Therapeutics received 510(k) clearance from the FDA for the Orbit subretinal delivery system (August 2020). The firm also received fast track designation from the FDA for its dry AMD gene therapy (September 2020). Finally, the firm announced a subject with geographic atrophy (GA) underwent a surgery using its proprietary Orbit Subretinal Delivery System (Orbit SDS) to deliver the company's investigational gene therapy, GT005 (October 2020).
- SparingVision is developing SPVN06 for the mutation-agnostic treatment of retinitis pigmentosa. SPVN06 is a AAV gene therapy consisting of one neurotrophic factor and one oxidative stress reducing enzyme (October 2020).

Other news about pharmaceutical and medical device firms

- Aerie received U.S. FDA approval to use their facility in Athlone, Ireland, to produce their ocular hypotensive product, Rhopressa® (netarsudil ophthalmic solution, September 2020). This process took five years.

Regulatory, government, and other research news

- Abcam, a life sciences firm, and the laboratory of Smaara Reck-Peterson, Ph.D .at the University of California, San Diego are donating funds to the Henrietta Lacks Foundation in recognition of their use of HeLa cells in research (August 2020).
- Ashtel studios issued a voluntary recall of licensed hand sanitizers due to misbranding because they resemble food and drink container pouches (October 2020).
- Bausch + Lomb and Eton Pharmaceuticals announced U.S. FDA approval for its Alaway® Preservative Free (ketotifen fumarate) ophthalmic solution, 0.035%, antihistamine eye drops (EM-100), as an over-the-counter (OTC) preservative-free product to temporarily relieve itchy eyes (September 2020). This firm entered into an agreement with Allegro Ophthalmics to acquire Allegro's ophthalmology assets, incluidng its risuteganib and ALG-1007 (September 2020). Bausch also licensed EyeNovia's microdose formulation of atropine ophthalmic solution, which is being investigated for the reduction of pediatric myopia progression (October 2020). Finally, this firm acquired an exclusive license for a myopia control contact lens design developed by BHVI (October 2020).

- California enacted SB 852, which allows requires its Health and Human Services Agency (CHHSA) to enter into partnerships to increase patient access to affordable drugs (September 2020).
- Gilead received U.S. FDA approval for its antiviral drug Veklury® (remdesivir) for use in adult and pediatric patients 12 years of age and older for the treatment of COVID-19 requiring hospitalization (October 2020). This product was formally approved in Taiwan.
- Marksana Pharma recalled lots of its Metformin Hydrochloride Extended-Release due to the detection of N-Nitrosodimethylamine (October 2020).
- Nevakar and Zhaoke Ophthalmology Pharmaceutical announced an exclusive licensing agreement for the development and commercialization of Nevakar's NVK-002 in Greater China. NVK-002 is an atropine product currently under clinical evaluation in the CHAMP study, a Phase 3 clinical trial being carried out in the US and Europe (October 2020).
- Ocular Therapeutix resolved a warning letter from FDA's Center for Device and Radiological Health (CDRH) reagrding its Resure® sealant (September 2020).
- Pfizer announced it will stop production of echothiophate iodide (Phospholine iodide®) ophthalmic solution (October 2020).
- Regeneron Pharmaceuticals submitted a request to the FDA seeking emergency-use authorization for its REGN-COV2 investigational antibody combination for the treatment of COVID-19. REGN-COV2 is a combination of two monoclonal antibodies, REGN10933 and REGN10987, which has been designed to block infectivity of SARS-CoV-2 (October 2020).
- Santen announced the launch of the Re-SOLVE Antibiotic Resistance initiative, which aims to lead the way in the fight against antibiotic resistance in ophthalmology (October 2020).
- Santen Pharmaceutical and Aerie entered into an exclusive development and commercialization agreement for Rhopressa® (netarsudil ophthalmic solution) 0.02% and Rocklatan® (netarsudil and latanoprost ophthalmic solution) in Japan, along with rights for several other Asian countries (October 2020).
- Santen will acquire Eyevance (September 2020).
- The Nature family of journals agreed upon a deal that will allow scientists at research institutions across Germany to publish papers in Nature and its 54 sister journals that are immediately free to read "transformative agreement" (October 2020) [42].
- U.S. FDA:
  - Is using a updated "Phonetic and Orthographic Computer Analysis" (POCA) Program to evaluate proposed brand names (August 2020).
  - Is requiring the boxed warning be updated for all benzodiazepine medicines regarding safety issues related to dependence and withdrawal (September 2020).
  - Released information on the Safe Importation Action Plan, with two pathways. Under Pathway 1, a Notice of Proposed Rulemaking ("NPRM") would rely on the authority in the Federal Food, Drug, and Cosmetic Act ("FD&C Act") section 804 to authorize demonstration projects to allow importation of drugs from Canada. The NPRM would include conditions to ensure the importation poses no additional risk to the public's health and safety and that it will achieve significant cost savings to the American consumer. Under Pathway 2, manufacturers could import versions of FDA-approved drug products that they sell in foreign countries that are the same as the U.S. versions. Under this pathway, manufacturers would use a new National Drug Code (NDC) for those products, potentially allowing them to offer a lower price than what their current distribution contracts require (September 2020).
  - Is proposing restricting compounding of moxifloxacin for intraocular use at outsourcing facility use (503b, August 2020). Several ophthalmology professional societies (American Academy of Ophthalmology, American Society of Cataract and Refractive Surgery, American Glaucoma Society, American Association for Pediatric Ophthalmology and Strabismus, the American Society of Retina Specialists, the Retina Society, the Macula Society, and the Cornea Society) are working to prevent this restriction.
  - Is proposing new regulations regarding "intended use" in determining if a potential product meets the definition of a drug or device and whether an approved or cleared medical product is intended for a new use (September 2020) [43].
- van der Naald et al tracked animal study protocols approved in the University Medical Center Utrecht in the Netherlands, to assess whether these have led to a publication with a follow-up period of 7 years. They found that 60% of all animal study protocols led to at least one publication (full text or abstract), covering 26% of the 5590 animals used. They conclude that there is a need for preclinical preregistration, in view of the risk of reporting and publication bias in preclinical research. They developed a platform dedicated to animal study protocol registration: www.preclinicaltrials.eu. (October 2020) [44].
- Vedere Bio was acquired by Novartis. The firms is advancing intravitreally administered photoreceptor-protein-based optogenetic gene therapies for vision restoration (October 2020).

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Gary D. Novack[a,b,*]
[a] *PharmaLogic Development Inc, San Rafael, CA, USA*
[b] *Department of Ophthalmology & Visual Sciences, University of California, Davis, USA*

[*] PharmaLogic Development Inc, San Rafael, CA, USA.
E-mail address: gary_novack@pharmalogic.com.