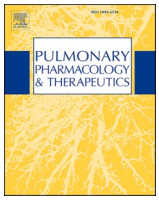
Pulmonary Pharmacology & Therapeutics 89 (2025) 102348

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt



Drug repurposing tactics in the USA: Known active pharmaceutical ingredients in new indications

ARTICLE INFO

Keywords:
Drug repurposing
FDA regulations
Compounding
Medication
Covid-19

In the broadest sense drug repurposing refers to the intentional reuse of known active pharmaceutical ingredients (APIs) that were contained within pharmaceuticals previously approved by the US Food & Drug Administration or other regulatory agencies for a specific medical indication into a new indication. The Covid-19 epidemic rapidly stimulated substantial interest by clinicians and scientists in the hopes of addressing an emergent disease with off-label prescriptions of drugs containing known APIs having de-risked safety profiles, thus providing compassionate care at a time of crisis. However, drug repurposing with the intention of potential commercial development is far more complex than merely prescribing off-label an approved medication [1]. Presented below are many of the important tactics to consider through the lens of the USA regulations, clinical investigations, and commercialization challenges, including recent examples.

Regulatory Frameworks: Four distinct regulatory pathways exist in the USA to pursue known APIs into new indications as repurposed prescription (Rx) medications (see Table 1), excluding drug-device combinations:

- *503A Compounding* yields medications within a state-licensed compounding pharmacy that is subject to USP 795 guidelines. The compounds must be prescribed to a named patient by a licensed medical practitioner.
- *503B Compounding* yields medications manufactured according to Good Manufacturing Practices (GMP) within outsourcing facilities. Products may only be distributed to clinics and hospitals.
- *505(b)(2)* registration pathway yields FDA pre-market approved medications produced according to GMP that rely upon prior publications and/or studies to reduce the scope of work during development. New indications, new formulations, and/or new API combinations are permitted. Approval is restricted to a specific medical indication.
- *505(b)(1)* registration pathway yields FDA pre-market approved medications produced according to GMP, using the thorough and very expensive drug development pathway for a novel chemical entity (NCE), i.e., not contained within a prior approved drug, although known APIs can also be used. Approval is restricted to a specific medical indication.

Table 1 summarizes the most relevant distinctions between the four options that investigators may select as tactical regulatory frameworks available for drug repurposing.

Clinical Investigations: Clinicians should first obtain proof-of-concept (POC) evidence of human efficacy in the new indication. Investigators should carefully consider the mandatory governmental regulations, institutional policies, and scientific/clinical journal policies. One often starts with a physician-sponsored POC study in a limited number of patients using either an off-label approved drug or a compounded drug. This is legally permissible at the discretion of the physician using her/his professional judgment relative to standard-of-care (SOC) treatments.

All patients must provide their consent to the public disclosure of their research results and be informed that his/her identity will not be disclosed. Institutional Review Board (IRB) approval is often not required for publishing single case reports or case series articles. Depending on the policies of research institutions and/or the selected journal for the publication, the number of human subjects in a case series might be arbitrarily limited, even though there are no US statutes limiting the number of subjects without requiring IRB approval. It is possible to publish case series articles with as many as eight subjects without IRB approval [2,3]. However, IRB approval of a prospective randomized controlled trial (RCT) is required, and IRB approval or exemption of a retrospective study is generally required. IRB committees have some discretion, but they might deem known APIs within the new context to be “experimental medications”, thereby requiring an FDA Investigational New Drug (IND) application or exemption.

The human clinical evidence can range from anecdotes upward to statistically significant RCTs that are appropriately powered by a statistician. The publications can range in quality and inference of veracity from minimal/poor (e.g., a case report), to better (e.g., a case series), to moderate (e.g., a well-defined large cohort study or a large retrospective association study), to solid/convincing (e.g., a well-designed and powered RCT). Placebos, randomization, blinding, and statistics help to abrogate biases of clinicians and/or patients. This is a serious problem in a world filled with social media-driven misinformation and anecdotes fueling confirmation biases, such as the perception by some that homeopathic treatments are effective, although they do not meet the

https://doi.org/10.1016/j.pupt.2025.102348
Received 3 January 2025; Received in revised form 13 February 2025; Accepted 28 February 2025
Available online 1 March 2025

Table 1
Regulatory frameworks for prescription drugs in the USA.

Activities:	503A compounding	503B compounding	505(b)(2)	505(b)(1)
GMP manufactured	no	yes	yes	yes
Known API or NCE	known API	known API	known API	NCE*
IND required	no	no	yes	yes
Rely on prior studies/ publications	optional	optional	yes	no
CMC approval	no	no	yes	yes
Animal safety & efficacy	no	no	optional	yes
Clinical Phase I	no	no	optional	yes
Clinical Phase II	no	no	yes	yes
Clinical Phase III	no	no	yes	yes
Indication specific	no	no	yes	yes
NDA pre-market approval required	no	no	yes	yes
Development cost ($ US)	$1 K+	$10 K+	$10 M+**	$100 M+**
Patented product	uncommon	uncommon	optional	yes
Product distribution	no	limited	yes	yes
Sales channel	named patient only	in-clinic use	pharmacies	pharmacies
Delivery via mail	yes	no	yes	yes

GPM – good manufacturing practice; known API – active pharmaceutical ingredient, i.e., contained within a prior FDA approved drug; NCE – novel chemical entity, i.e., not contained within a prior approved drug; (*) also possible to use a known API; IND – investigational new drug application; CMC – chemistry, manufacturing, and controls; NDA – new drug application. Note that cost estimates are based upon the author's experience or (**) Longsworth et al., 2018.

stringent statistical evidence of efficacy, as they essentially mirror the placebo effect [4]. Furthermore, the level of the POC evidence in support of a repurposed drug is dependent on the availability of research funding and the expertise of the research team.

Recent Examples of Drug Repurposing: When Covid-19 emerged in the USA in early 2020 as an epidemic, drug repurposing suddenly became trendy. The author and colleagues published within months on a physician-sponsored POC study of a cohort of 110 high-acuity hospitalized patients afflicted by SARS-CoV2, who were effectively treated with dual antihistamines, cetirizine plus famotidine [5]. By reducing the pulmonary cytokine storm, two very safe antihistamines reduced symptom severity and likely spared the lives of some severe and critical in-patients relative to SOC, as reported for other similar cohorts of high-acuity patients at that early timepoint.

At this same juncture two other repurposed medications were fiercely advocated for and used off-label by countless Covid-19 patients, namely hydroxychloroquine and ivermectin. Neither drug has been demonstrated to be effective in large cohort, large association, or RCTs [6,7]. However, both drugs were politically and sociologically expedient, even though other treatment alternatives existed.

As other examples of drug repurposing outside of pulmonology, patients afflicted with interstitial cystitis were treated with compounded cetirizine plus famotidine once daily [8]. This POC study revealed reductions in the severity of bladder pain and urination symptoms, thereby improving quality of life in treatment-refractory patients. And, in physician-sponsored studies to discover a compounded non-benzodiazepine anti-anxiety treatment, atenolol plus scopolamine produced a rapid calming effect, thus meeting the objective of a new class of *prn* anxiolytic medications [2,3,9].

These examples indicated that off-label medicines or compounds having single or dual known APIs have been proposed as new therapies and backed by POC publications.

Commercialization: A defensible business case for a repurposed medication extends well beyond off-label prescribing, as there are many factors to consider: (a) Are there any peer reviewed publications as evidence of efficacy in the new indication?; (b) Is the technology patentable? Patent searches to determine novelty, non-obviousness, and freedom-to-operate are imperative for any business proposal involving any regulatory approval via the 505(b)(2) or 505(b)(1) pathways. Patentability when using known APIs is especially challenging in view of ample prior art disclosures, although it is sometimes possible with Claims-wordsmithing skill to obtain patents.; (c) Do you possess the rights to any issued patent Claims protecting the formulation technology to enable a new route of administration to facilitate the new indication and/or extend market exclusivity?; (d) Can the product address a rare or orphan disease indication, thereby possibly reducing development cost and extending market exclusivity?; And, (e) is the clinical development and commercialization strategy bankable with investors or potential corporate partners?

Repurposed 505(b)(2) drugs are not appealing as acquisitions by Big Pharma firms, which rely heavily upon patented NCEs, the 505(b)(1) pathway, and ample cash. The development costs alone for an NCE can be hundreds of millions of dollars, depending largely upon the registration trials hurdles [10]. However, Big Pharma firms will opportunistically generate repurposed drugs based upon patented active ingredients that they own. A financially successful repurposed medication that is representative of this approach is minoxidil. It was an NCE originally approved as an oral medication for hypertension and thereafter repurposed as a topical formulation for hair growth, i.e., Rogaine® [11,12].

Repurposed 505(b)(2) drugs are much more affordable to develop (e.g., $10+ million) [10], thus are attractive to (mid-sized) specialty pharmaceutical firms. These products benefit from: (a) bypassing early-stage drug discovery; (b) de-risked known APIs with historic safety profiles; (c) reduced clinical development cost; and (d) acceptance of more modest advertising expenditures and sales projections. These features make the return-on-investment appealing to mid-sized firms and investors.

In view of these pharmaco-economic issues, in many cases a repurposed medication is best suited only for compounding via 503A and/or 503B tactics, and that is OK. However, compounds are substantially limited in reaching large numbers of patients, because they are not FDA-approved medications, cannot make claims of efficacy and safety, and the distribution channels open to FDA-approved drugs do not apply. But compounds are legal prescription medications and can serve as low-cost repurposed drugs to generate low-to-modest product sales. Compounds backed by issued patents and POC publications can be attractive as acquisition targets by specialty pharmaceutical firms, with the intention of further clinical development.

One must consider the entire development program and costs with an eye toward an optimal regulatory framework and the pharmaco-economics at commercialization. Summarized herein are the major issues that one is likely to encounter while attempting to create prescription medications using known APIs in new indications.

Funding

The author did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The author discloses that he is: (a) the inventor of four issued anxiolytic drug patents in North America assigned to Magnolia CNS LLC, and a licensee to Magnolia CNS LLC; and (b) a co-inventor of an anti-

inflammatory drug patent application assigned to Hista Rx LLC, and a shareholder in Hista Rx LLC, which has an issued patent in the UK and Europe.

Acknowledgements

The author acknowledges gleaning insights on drug repurposing from Fred Dechow, Doug Nesbitt, Doug Paul, and former colleagues in Upjohn, Southern Research, IntegriDerm, MediQuest Therapeutics, and Trends in Pharma Development.

Data availability

No data was used for the research described in the article.

References

[1] Y. Cha, et al., Drug repurposing from the perspective of pharmaceutical companies, Br. J. Pharmacol. 175 (2) (2018) 168–180.
[2] A.B. Benjamin, T.P. Dooley, Anxiolytic benefits of compounded atenolol - scopolamine in eight patients in psychiatry, Per. Med. Psychiatry 19–20 (2020) 100051.
[3] T. Thomas, T.P. Dooley, Treatment of anxiety prior to a medical procedure using an atenolol - scopolamine combination drug, J. Depress. Anxiety 7 (2) (2018) 303.
[4] E. Ernst, A systematic review of systematic reviews of homeopathy, Br. J. Clin. Pharmacol. 54 (6) (2002) 577–582.
[5] R.B. Hogan II, et al., Dual-histamine receptor blockade with cetirizine - famotidine reduces pulmonary symptoms in COVID-19 patients, Pulm. Pharmacol. Therapeut. 63 (2020) 101942.
[6] S. Naggie, et al., Effect of higher-dose ivermectin for 6 Days vs placebo on time to sustained recovery in outpatients with COVID-19: a randomized clinical trial, JAMA, J. Am. Med. Assoc. 329 (11) (2023) 888–897.
[7] C.G. Recovery, et al., Effect of hydroxychloroquine in hospitalized patients with covid-19, N. Engl. J. Med. 383 (21) (2020) 2030–2040.
[8] R.B. Hogan II, et al., Treatment and maintenance of interstitial cystitis/bladder pain syndrome in female patients with ceterizine-famotidine: a case series, Case Rep. Clin. Med. 12 (2023) 61–71.
[9] T.P. Dooley, A.B. Benjamin, T. Thomas, Treating anxiety with a beta blocker - antimuscarinic combination: a review of compounded atenolol - scopolamine, Clin. Psychiatr. 5 (3) (2019) 63.
[10] G. Longsworth, A. Wang, D. Varughese, The 505(b)(2) drug approval pathway: a Potential solution for the distressed generic pharmaceutical industry in an increasingly diluted ANDA marketplace? Pharm. Law Ind. Rep. 16 PLIR 371 (2018).
[11] T.P. Dooley, et al., Localization of minoxidil sulfotransferase in rat liver and the outer root sheath of anagen pelage and vibrissa follicles, J. Invest. Dermatol. 96 (1) (1991) 65–70.
[12] T.P. Dooley, Molecular biology of the human phenol sulfotransferase gene family, J. Exp. Zool. 282 (1–2) (1998) 223–230.

Thomas P. Dooley
Trends in Pharma Development, 270 Skyline Drive, Trussville, AL, 35173, USA
E-mail address: tom@tomdooley.org.