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REVIEW ARTICLE

Patient-Centric Strategies for Drug Re-innovation

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Abstract
Drug repurposing, often achieved via the FDA's 505(b) (2) pathway, is an increasingly popular approach in today's pharmaceutical environment. Repurposing or "re-innovation" comprises a multitude of techniques, which have resulted in wide-ranging commercial success. This article explores the diverse strategies that have been taken to repurpose drugs, and distinguishes a unifying theme among the most commercially successful examples—the ability to address significant unmet needs. The examples listed in this paper relate to small molecules drugs and certainly not exhaustive, however provide some of the key strategies that have been successful using "re-innovation" pathway.

Keywords Re-innovation · Repurposing strategies · Life-cycle management · Generic · Brand products

Introduction

Today's pharmaceutical industry faces intense competition, rising R&D expenses, and heightened pricing pressures. Generic drugs account for 88% of all prescriptions filled in the USA today and, according to Quintiles IMS, may account for 91–92% of prescription volumes by 2020 [1]. However, the generic drug sector, in particular, is confronted with substantial challenges. Unprecedented levels of competition exist due to increasing penetration from China and India in the US market. For example, in 2017, Chinese generic manufacturers gained approval for 38 generic drug applications, nearly doubling the number from 2016 [2]. Expedited reviews of drug applications and reduction of regulatory hurdles, as facilitated by the FDA's Drug Competition Action Plan, have further encouraged generic competition [3]. Additionally, wholesalers, drugstores, and pharmacy benefit managers have consolidated to form "mega buyers" or general purchasing organizations that command significant discounts, further intensifying pricing pressure for generic manufacturers.

To thrive in such an environment, drug repurposing or re-innovation has emerged as a viable solution. Re-innovative products are defined as those which "provide new features, benefits, or improvements through existing technology" [4]. For generic drug companies, introducing differentiated products via drug repurposing enables competition on the basis of product quality rather than price [4]. For innovative drug companies, drug repurposing permits reduced development time, cost, and risk as compared to new chemical entities.

Repurposed drugs, such as new strengths, formulations, indications, routes of administration, and dosing regimens of existing drug products are generally captured under the US FDA's 505(b) (2) regulatory pathway (Fig. 1). Per the Food, Drug and Cosmetic Act, a 505(b) (2) application is one for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" [5] (21 U.S.C. 355(b) (2) CFR code of Federal regulations).

Although this pathway generally confers higher investment and technological barrier than a generic drug filing, benefits for the drug manufacturer include potential market exclusivity and patent protection [6]. Furthermore, drugs that are repurposed to better meet the needs of patients, payers, or healthcare providers may capture higher market share and enjoy premium pricing compared to conventional generic drugs [7]. Key differences between drug regulatory pathways are highlighted in Table 1.

Investment in enhanced versions of existing drugs is an emerging and rapidly growing strategy for portfolio differentiation and fortification in today's dynamic pharmaceutical landscape [8]. In

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Fig. 1 Examples of 505(b) (2) approaches

2017, the FDA approved more 505(b) (2) applications than ever before in its history [9]. The number of such approvals (63) represents a 40% increase over the prior year, and exceeds the number of novel drug approvals by more than 25% [9] (Fig. 2).

Table 1 FDA drug regulatory pathways

Application type	New drug application (NDA)/505 (b) (1)	New drug application (NDA)/ 505 (b) (2)	Abbreviated new drug application (ANDA)
Application content	Contains full reports of investigations of safety and efficacy	Contains full reports of investigations of safety and efficacy but at least some of the information required for approval comes from studies not conducted by or for the applicant	Contains information to show that the proposed product is bioequivalent to a previously approved product
Exclusivity opportunities	3-year clinical 5-year NCE 7-year ODE 6-month PED 5-year GAIN	3-year clinical 7-year ODE 6-month PED 5-year GAIN 5-year NCE	180-day patent challenge
Approximate development time	5–15 years	2–10 years	1–3 years
Commercial considerations	Requires promotion	May require promotion	Typically does not require promotion
Relative risk, cost, and ROI	High	Moderate	Low

For details on acronyms please refer to Appendix Table 3

Investment in enhanced versions of existing drugs, or so-called super-generics, new therapeutic entities, or value-added generics, or re-innovation—is an emerging strategy for portfolio differentiation and fortification in today's dynamic pharmaceutical landscape [8].

Value-Centric Design

Drug repurposing encompasses a broad array of potential alterations including modified routes of administration, strengths, indications, pharmacokinetics, etc. (Fig. 1). The commercial viability of such products is as wide-ranging as the approaches themselves. Though seemingly intuitive, the most successful examples of repurposed drugs *address unmet needs that impact patients, providers, and healthcare systems*—that is, *they are* "*value-centric*." Such drugs ultimately impact health economics by reducing hospitalization rates or improving disease management with cost-effective treatments. The remainder of this article explores some of the key examples *(summary included in* Table 2 *in the appendix)* of successful value-centric drug re-innovation.

Patient Convenience and Compliance

Some of the most commercially successful 505(b) (2) products are those which produce value for the patient, improving their experience and ultimately driving compliance.

Mitigating Food Effects

Isotretinoin is a widely prescribed treatment for severe, nodular acne, but typical treatments (Roche's Accutane®[1] and equiva-

[1] Accutane is a registered trademark of Hoffmann-La Roche Limited; Absorica is a registered trademark of Ranbaxy Laboratories Inc.; Lidose is a trademark of Galephar Pharmaceutical Research, Inc.; Jentadueto XR is a registered trademark of Boehringer Ingelheim; Zubsolv is a registered trademark of Orexo US, Inc.; Suboxone is a registered trademark of Indivior (UK) Limited; Ulceris is a registered trademark of Valeant Pharmaceuticals International, Inc.; MMX is a registered trademark of Intel Corp.; Abraxane is a registered trademark of Abraxis BioScience, LLC; Cremophor is a registered trademark of BASF SE; Vimovo is a registered trademark of AstraZeneca UK Limited; Xtampza ER and DETERx are registered trademarks of Collegium Pharmaceutical, Inc.; Bendeka and Treanda are registered trademarks of Cephalon, Inc.; Exparel and DepoFoam are registered trademarks of Pacira Pharmaceuticals, Inc.; Voltaren Gel is a registered trademark of Novartis AG; Doryx MPC is a registered trademark of Mayne Pharmaceuticals; Monodox is the registered trademark of Aqua Pharmaceuticals, LLC; Onzetra is a registered trademark of Avanir Pharmaceuticals, Inc.; Imitrex is a registered trademark of the GlaxoSmithKline group of companies; and Vyvanse is a registered trademark of Shire LLC

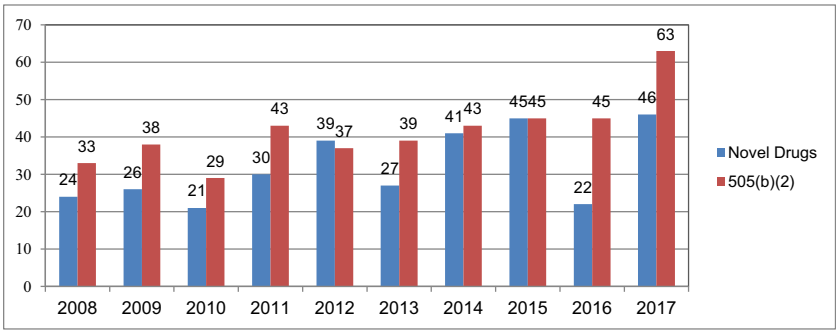

Fig. 2 New drug approvals by year; US FDA approvals for novel drugs and 505(b) (2) drug applications by year [9, 10] (Novel molecules includes small molecules only)

lents) require dosing with a high-fat meal. In the absence of high-fat food, the drug's absorption is limited and efficacy may be compromised. To mitigate isotretinoin's food effect and enable greater dosing flexibility, Cipher Pharmaceuticals developed Absorica®. This product, currently marketed by Sun Pharma, is formulated with highly lipophilic Lidose™ capsule technology, which enhances absorption by 83% under fasted conditions [11]. Under high-fat, fed, conditions, the rate and extent of absorption is equivalent to Accutane® [12]. Therefore, patients have the flexibility to take the re-formulated product with or without food. According to IMS, sales for this product were over $320m in 2016 (MAT Feb 2016).

Reducing Pill Burden

Treatment of type II diabetes mellitus typically includes metformin (of the biguanide class) in combination with a secondary therapy, such as DPP4 inhibitors ("gliptins") or SGLT2 inhibitors ("flozins"). In 2012, Boehringer Ingelheim, in collaboration with Eli Lilly, launched Jentadueto®, a fixed-dose combination of metformin and linagliptin. According the product's prescribing information, clinical trials demonstrate that linagliptin co-administered with metformin "provided statistically significant decrease in blood glucose compared with linagliptin alone in treatment-naïve adults…" (https://investor.lilly.com/releasedetail.cfm?ReleaseID=863912). Having a twice-daily fixed-dose combination reduces the patients' pill burden, which may be substantial for this population. Furthermore, a once-daily formulation (linagliptin and metformin extended release) was approved by FDA in May 2016. According to IMS, sales for Jentadueto® exceed $200m (MAT Feb 2017).

Improving Palatability

The combination of buprenorphine and naloxone is commonly prescribed for maintenance treatment of opioid dependence. Burpenorphine, a partial opioid agonist, produces analgesic effects while rendering receptors inactive. Naloxone, an opioid antagonist, counteracts the limited stimulation associated with buprenorphine. Various formulations of this combination are marketed in the USA including sublingual tablets, sublingual films, and buccal films. In 2013, Orexo launched Zubsolv®, a sublingual tablet formulation which boasts features that are "patient-preferred" (https://www.zubsolv.com/zubsolv/patient-preferred/). In a clinical trial "77.5% of patients preferred the taste of Zubsolv® to Suboxone® film. Zubsolv® is the only sublingual tablet for the treatment of opioid dependence that has a menthol flavor" (https://www.zubsolv.com/zubsolv/patient-preferred/). Zubsolv® is also available as a small tablet with lower dose. "Because of its highly efficient delivery system, a greater percentage of the medication in Zubsolv® tablets gets into the bloodstream than with Suboxone® tablet" (https://www.zubsolv.com/zubsolv/patient-preferred/). According to IMS, sales for Zubsolv® exceed $140m (MAT Feb 2017).

Optimizing Delivery

Budesonide is a glucocorticosteroid used for treatment of mild-to-moderate ulcerative colitis. Delivery to the site of action (the lumen of the colon) was previously achieved using rectal suppository formulations directly in contact with the colonic mucosa. In 2013, Salix Pharmaceuticals (now Valeant) launched Uceris®, a once-daily, controlled-release oral tablet formulation of budesonide which "uses MMX® technology, which is designed to target delivery of budesonide throughout the full length of the colon for localized treatment of active UC" (https://www.salix.com/products/uceris-tablets). This formulation provides easier and more comfortable administration than the rectal suppository, and currently enjoys sales over $200m (IMS MAT Feb 2017).

Improving Patient Safety

In addition to enhancing the patient experience by improving convenience and/or compliance, product modifications that increase safety have proven commercially valuable.

Minimizing Adverse Events

One of the most successful examples of drug re-innovation is Celgene's nanoparticle albumin-bound version of paclitaxel—Abraxane®. According to Celgene's website, Abraxane® was studied in a phase III trial vs. an established regimen (http://abraxane.com/hcp/metastatic-breast-cancer/efficacy/trial-design/trial-design/). Because Abraxane® uses albumin to deliver the chemotherapy rather than emulsifier like Cremophor, there is "no standard pre-medication for hypersensitivity required" (http://abraxane.com/hcp/metastatic-breast-cancer/efficacy/trial-design/trial-design/). The label also compares hypersensitivity and other adverse events vs. standard paclitaxel (http://abraxane.com/hcp/metastatic-breast-cancer/efficacy/trial-design/trial-design/), highlighting improvements in percentage of patients with hypersensitivity reactions and injection site pain. Consequently. Abraxane® has overtaken more than 95% of the overall paclitaxel market sales and earns more than $600m according to IMS (MAT Feb 2017).

Another "re-innovative" product which is intended to minimize adverse events is Vimovo®, an oral, fixed-dose combination of naproxen, a non-steroidal anti-inflammatory drug (NSAID) and esomeprazole magnesium, a proton pump inhibitor (PPI). The combination of NSAID and PPI is designed to offer "added gastro protection" to patients at risk of developing NSAID-associated ulcers (http://www.vimovo.com/). The tablets are comprised of an outer layer of esomeprazole, designed for immediate release, and a delayed-release, pH-sensitive layer of naproxen, intended for release only in the presence of decreased gastric acid (http://www.vimovo.com/). This novel fixed-dose combination has sales over $600m (IMS MAT Feb 2017).

Deterring Abuse

In addition to minimizing adverse events, "re-innovative" products may enhance patient safety by deterring abuse. With the ongoing opioid epidemic in the USA, FDA is concerned with drug abuse, diversion, and misuse and has issued regulatory guidance on abuse-deterrent opioid formulations. Collegium Pharmaceutical's Xtampza ER® is an extended release, oral capsule formulation of oxycodone, which utilizes patented abuse-deterrent technology called DETERx®. According to Collegium, the DETERx® formulation comprises of an oxycodone base with inactive ingredients to form a lipophilic salt. "The chemical properties of this lipophilic salt permit homogeneous distribution of the active drug in each waxy microsphere… DETERx® technology is designed to avoid rapid increases in plasma concentrations from crushing, chewing, snorting—and also resists injection and extraction" (http://www.xtampzaer.com/hcp/deterx-technology.html#tab-2). The product, which was recently launched in 2016, currently has sales over $10m (IMS MAT Feb 2017) and is expected to grow.

Providing Value to the Healthcare System

The aforementioned examples highlight products designed to improve the experience of the patient. Other successful 505(b)(2) products have addressed the overall costs and experience of the healthcare system or institution. Bendamustine is indicated for chronic lymphocytic leukemia and Indolent B cell non-Hodgkin lymphoma (http://bendeka.com/about-bendeka). BENDEKA® from Cephalon. Inc. is a ready-to-dilute version of TREANDA® which contains Bendamustine in lyophilized form (http://www.treandahcp.com/). BENDEKA® enables rapid infusion, potentially reducing dosing errors. It is also provided in multi-dose vials with extended stability. The product, which was recently launched in 2016, currently has sales of $555m (IMS MAT Jul 2017) and is expected to grow.

Modifying Release Profile

Pacira Pharmaceuticals markets Exparel®, an extended-release formulation of bupivacaine, a local anesthetic, indicated for postsurgical analgesia (http://www.exparel.com/index.shtml). Exparel® is formulated with DepoFoam® technology, a lipid-based drug delivery system intended to slowly deliver bupivacaine and extend its pharmacological effect (http://www.exparel.com/index.shtml). Consequently, Pacira states that a single dose of Exparel® may reduce opioid consumption (though this has not been demonstrated in pivotal and clinical trials) and "eliminates the need for catheters and pumps that may hinder recovery" (http://www.exparel.com/index.shtml). The product, which was recently launched in 2012, currently has sales of $277m (IMS MAT Jul 2017) and is expected to grow.

New Strengths

Topical products often follow the 505(b)(2) pathway for novel strengths and indications. Extensive safety studies may be circumvented, as the 505(b)(2) pathway leverages existing data from an original NDA. Often such data may be available as part of dose ranging studies during pharmacokinetics and pharmacodynamics evaluation from the original drug development. Such new strengths may be applicable for new indications, new dosing regimens, or expansions to the pediatric segment. Examples include diclofenac and doxycycline.

VOLTAREN® GEL (Diclofenac 1% Gel) (https://dailymed.nlm.nih.gov/dailymed/medguide.cfm?setid=60045fc6-f0d9-4f67-ba91-c3b317596437) is a non-steroidal anti-inflammatory drug indicated for the relief of the pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands. Another product, Solaraze®, contains 3% diclofenac gel and is indicated for the topical treatment of actinic keratoses (AK) (https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021005s013lbl.pdf).

Doryx MPC (Doxycycline Delayed Release Tablets, 60 and 120 mg) is indicated for Rickettsial infections, sexually transmitted infections, respiratory tract infections, specific bacterial infections, ophthalmic infections, Anthrax, etc. (http://www.doryx.com/). Another product, Monodox® (Doxycycline Capsules, 100, 75, 50 mg) is indicated for Gram negative bacteria, Gram positive bacteria, Anaerobic bacteria, other bacteria, parasites, etc. (http://www.aquapharm.com/monodox.php).

Drug-Device Combinations

In addition to new formulations and strengths, the 505(b) (2) pathway may be employed for approval of drug-device combinations, where the original drug safety and toxicity data may be leveraged. For example, intranasal sumatriptan allows more rapid drug absorption than other marketed forms. Within 48 h of an initial dose of ONZETRA® (a device delivering sumatriptan intranasally), 63% of subjects did not take another dose or additional medication (vs 48% on placebo) (https://www.onzetra.com/). For treatment of migraines, reaching the peak plasma concentration is critical, as migraine attacks often have debilitating effects on patients' lives (https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en /Prescribing_Information/Imitrex_Nasal_Spray/pdf/IMITREX-NASAL-SPRAY-PI-PIL.PDF).

Pro-drugs

Designing a new drug is costly, time-consuming, and risky. One attractive option to differentiate from currently marketed products is to chemically modify the characteristics of an existing drug by creating a pro-drug. A pro-drug is inactive in its current form and therefore requires metabolic conversion after administration to become pharmacologically active. Pro-drugs may offer advantages including enhancing bioavailability and targeting drug delivery to specific sites. By improving how selectively the drug interacts with cells or processes that are not its intended target, doses may be reduced and side effects may be minimized. Pro-drug strategy can also leverage 505 (b) (2), by using data from original drug. This can help reduce costs, time, and risks. As the first chemically formulated pro-drug stimulant, lisdexamfetamine represents a new class of long-acting agents for the treatment of attention deficit hyperactivity disorder (ADHD). Vyvanse® (lisdexamfetamine dimesylate) offers prolonged efficacy with once-daily dosing along with low rates of inter-patient and intrapatient pharmacokinetic variability, reduced food and drug interactions, and possibly a lower potential for abuse or diversion (http://www.vyvanse.com/).

Conclusions

Drug repurposing is an increasingly popular and practical approach for creating value in the competitive pharmaceutical space. Typically, product re-innovations are categorized under US FDA's 505(b) (2) regulatory pathway which may help minimize complex clinical studies and reduce development timelines. Product re-innovations encompass numerous strategies including new strengths, formulations, indications, routes of administration, and creation of drug-device combinations and pro-drugs. Despite the approach, the fundamental characteristic of a successful product re-innovation is *the ability to fulfill unmet needs while creating value to key stakeholders*. In addition to ensuring that product design is patient-centric, product re-innovations should create value for two additional key stakeholders in the healthcare ecosystem: physicians/caregivers and payers. While the current article reviews various strategies which have historically proven to be commercially successful, it is critical that appropriate market research, market access, or Health Economics Outcomes Research (HEOR) is conducted to quantify the stakeholder benefits. Re-innovation strategy should be based on multiple factors; starting with identifying unmet meet patient need followed by classifying target product profile, evaluating development/clinical strategy, performing competitive analysis of existing products along with payer and reimbursement models, and generating/leveraging intellectual property. Value-centric strategies which address unmet needs have the potential for sustainable commercial success.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Appendix

Table 2 Summary of the key re-innovation examples discussed in article

Product	Drug(s)	Company	Type of re-innovation	Patient-centric impact	Therapeutic area	Approximate peak annual sales (IMS) (in mUSD)
Abraxane	Paclitaxel	Celgene	New formulation; nanoparticle albumin bound	Minimizing adverse events; enhancing efficacy	Oncology; breast cancer	$682
Absorica	Isotretinoin	Cipher/Ranbaxy	New formulation	Improved dosing; mitigates food effect	Acne	$320
Bendeka	Bendamustine	Teva (Eagle)	New formulation	Improving hospital treatment—reduces infusion time	Cancer	$491
Duexis	Ibuprofen/famotidine	Horizon	New combination	Minimizing adverse events	Arthritis pain	$972
Epiduo Forte	Adapalene benzoyl peroxide	Galderma	New strength	Enhanced efficacy	Acne	$130
Exparel	Bupivacaine	Pacira	New formulation; extended release	Improving hospital treatment—improved formulation—long-acting	Post-operative pain	$271
Jentadueto	Linagliptin/metformin	Boehringer Ingelheim	New combination	Improved dosing	Diabetes	$202
Uceris	Budesonide	Salix	New formulation; rectal foam	Improved dosing	Ulcerative colitis	$209
Vimovo	Naproxen/esomeprazole	AstraZeneca and Aralez	New combination	Minimizing adverse events	Arthritis pain	$612
Zubsolv	Buprenosphine/naloxone	Orexo	New formulation	Improved dosing—taste	Opioid addiction	$138

Table 3 Glossary of acronyms in Table 1

Acronyms	Full form	Comments
NCE	New Chemical Entity	NCE, according to the U.S. Food and Drug Administration, a drug that contains no active moiety that has been approved by the FDA in any other application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act
ODE	Orphan Drug Exclusivity	Granted to drugs designated and approved to treat diseases or conditions affecting fewer than 200,000 in the USA (or more than 200,000 and no hope of recovering costs
PED	Pediatric Exclusivity	Grants an additional 6 months of market protection at the end of listed patents and/or exclusivity for sponsor's drug products containing the active moiety, when the sponsor has conducted and submitted pediatric studies on the active moiety in response to a Written Request from FDA
GAIN	Generating Antibiotic Incentives Now	Grant an additional 5 years to certain exclusivity periods for products that have been granted a Qualified Infectious Disease Product (QIDP) designation (with some exceptions).

References

1. Suchak R, Murray LJ. Generic portfolio management: a paradigm for minimizing risk and maximizing value. Journal of Generic Medicines. 2016;13:63 http://journals.sagepub.com/doi/abs/10.1177/1741134316677850.
2. Financial Times https://www.ft.com/content/6645b174-2371-11e8-ae48-60d3531b7d11
3. US FDA https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm591184.htm
4. Barei F, Le Pen C, Simoens S. The generic pharmaceutical industry: moving beyond incremental innovation towards re-innovation. Generics and Biosimilars Initiative Journal (GaBI Journal). 2013;2(1):13–9.
5. Center for Drug Evaluation and Research (CDER). Guidance for industry: applications covered by section 505(b)(2). 1999. http://www.fda.gov/downloads/Drugs/Guidances/ucm079345.pdf.
6. Sario N. Prescription Drug Market: The World Is Turning to Generics; Part 5 of 17: Specialty Generics: Why are they getting more attention? 2015. http://marketrealist.com/2015/03/specialty-generics-getting-attention/
7. Barei F, Ross M. The refinement of the super generic concept: semantic challenge for product re-innovation? Generics and Biosimilars Initiative Journal (GaBI Journal). 2015;4(1):25–32.
8. Regulatory Affairs Professional Society. 2015. http://www.raps.org/Regulatory-Focus/News/2015/04/08/21933/An-Increasing-Number-of-Companies-Are-Using-a-Once-Obscure-FDA-Drug-Approval-Pathway/.
9. Camargo. https://camargopharma.com/2018/01/2017-505b2-nda-approvals-increase-dramatically-and-review-times-decrease/
10. New Drugs are FDA https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/default.htm
11. ABSORICA®. http://absorica.com/ Accessed October 25, 2017.
12. ABSORICA® Patient Brochure. http://absorica.com/patient-brochure.pdf". Accessed October 25, 2017.