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Drug Repurposing: Risk- Benefits and Associated Incentives

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ABSTRACT

Pharmaceutical R&D is failing with an era of triple obstacles – increased timelines for approval, high cost and even higher failure rates. The world around us is constantly putting pressure on creating completely new solutions for about 4000 diseases with known molecular basics and many other diseases without basic intellect. There comes a need to remove the wide gap in innovation showcasing a challenge for drug discovery. The shockingly tedious drug development process is forcing us to find more effective solutions and drug repurposing can be a starting point where the clear understanding of the de novo pathway for an existing drug essentially unlocks the full potential for repurposing a drug for other diseases. Drug repositioning (also known as drug repurposing, re-profiling, re-tasking or therapeutic switching) is the application of known drugs and compounds to new indications (i.e., new diseases). This idea dates back with cases like Viagra, Thalidomide, and Aspirin etc. There are a number of approaches to drug repurposing, but these are ultimately an expedition into new area. Scientists have to justify examining a compound in a different disease state, so they often make a hypothesis based on possible associations between mechanisms. A significant advantage of drug repositioning over traditional drug development is that since the repositioned drug has already passed a significant number of toxicity and other tests, its safety is known and the risk of failure for reasons of adverse toxicology are reduced. The possibilities are endless, and animal models are elevating drug repurposing's potential.

Keywords: Drug Repurposing, New indications, de-novo pathway.

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INTRODUCTION

The number of new drugs approved per billion US$ spent on R&D has halved roughly every nine years since 1950. With increase in the number of technical advances, since 1950 till today developing new drugs should have been much cheaper than estimated trajectory but in reality it has taken an inverse track.

An article in Nature effectively points on four possible primary reasons for the decline in the R&D productivity as:

Better than the Beatles problem

A new drug that is much better than the old one is only acceptable. It's very toilsome for a new pop song to get accepted unless and until it is much better than the Beatles. With the reality in focus that today's sizzler drug is tomorrow's inexpensive generic, there is no value in discovering something that is only just as good as the earlier version.

Cautious regulator

Constrained regulatory ratchet that rarely relaxes. For every actual and comprehended violation by the industry or real drug misfortune, the ratchet tightens on the regulatory agency relaxes it very seldom provided there is not any substantial risk to the drug safety.

Throw money at it tendency

Interminable string of the resources and money into a project till the mystifying puzzle unfolds and arrows the destination. The chances of outright success are elite. Burdens of thousands of the failed drug candidates on the one successful victor after discovery.

Basic research- brute force bias

If the drug being tested fails to show the explicit effect prognosticated, then the trial conks out implicating the narrow clinical research strategy. And thus "opportunities for serendipity are actively engineered out of the system".[1]

Drug Repositioning is the process of finding new uses of existing drugs outside the scope of the original indication. It is variously referred as "Drug Repositioning, Redirecting, Repurposing and reprofiling".

IS PHARMACEUTICAL R&D FLUNKING?

It's no secret that drug development is a challenging way to make profit. But behind every successful "BLOCKBUSTER" cover story of drugs with broad demographic indications and for every drug that achieves market approval from regulatory authorities, hundreds of millions of

dollars are spent on thousands of compounds that fail to make it to market as they washout in preclinical phase and hundreds more that fail in clinical trial.[2]

The course of Least Immunity: Repositioned Drugs - Stages in Drug Discovery

Discovery	New compounds are screened and identified	Target discovery and validation, lead identification by high throughput screening, lead optimization (development of the most drug gable compounds from the lead compounds)
Preclinical stage	The compounds are tested *in vitro* and in animal models	Analysis of pharmacological safety and efficacy in animals
Clinical development	The drug candidates are tested in human beings as clinical trials	Analysis of pharmacological safety, efficacy and drug interaction studies in humans

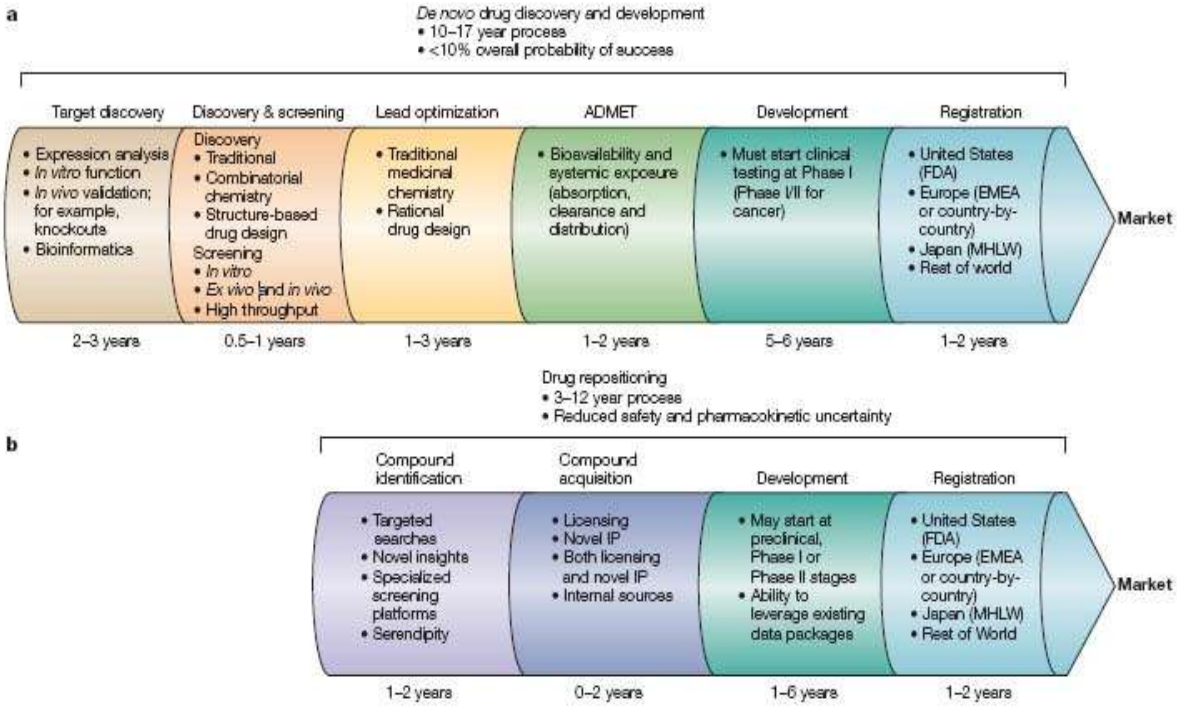

Figure 1: A comparison of traditional De-novo drug discovery and development Vs Drug Repositioning

With the pull back of preclinical trials not being capable of guarantying the usefulness of a compound in human beings due to physiological differences among humans and animals, there arises the uncertainty even for the most promising compound. Hence the two attritions for failure are the serious adverse events and decreased efficacy during clinical trials in humans. Therefore, the high risk reward trade-off in drug discovery and development is a major issue in new drug development and marketability.[3]

Moore's law into Eroom's law:

Unprecedented trends: Moore's law that button holes the rapid pace of technological innovation when applied to pharmaceutical domain turned Eroom's law. Despite huge advances in scientific, technological and managerial factors over the past 60 years that should assist in increasing the pharmaceutical research and development, there is a decline in the number of NME (New Molecular Entities) reaching market.

Impact of Triple frustration on R&D productivity

In an era of 'Triple frustration" with long drug-development timelines, sleep costs and high failure rates that have increasingly hexed the pharmaceutical industry, R&D productivity is the relationship between the value of a new drug (commercial and medical) and the investments required to develop this drug. Incorporating the key elements work in progress (WIP), Probability of technical success (PTS), value (V) in the nominator and the cycle time (CT) in the denominator, R&D productivity (P) can be described as in the adaptation of the pharmaceutical value equation.

$$P = (WTS \times PTS \times V) \div (CT \times C)$$

Increasing WIP, PTS or V of a new medicine will increase R&D productivity while increasing CT or C will decrease it and vice versa.

With a purview to the main phases of drug development, high throughput screening (HTS) , Hit-to-lead, preclinical and clinical, the clinical phases II and III have proven to be the most challenging as in these phases drugs often fail due to lack of Efficacy or low safety margins. The combine success rate of phase III and approval has even fallen to 50% in recent years.

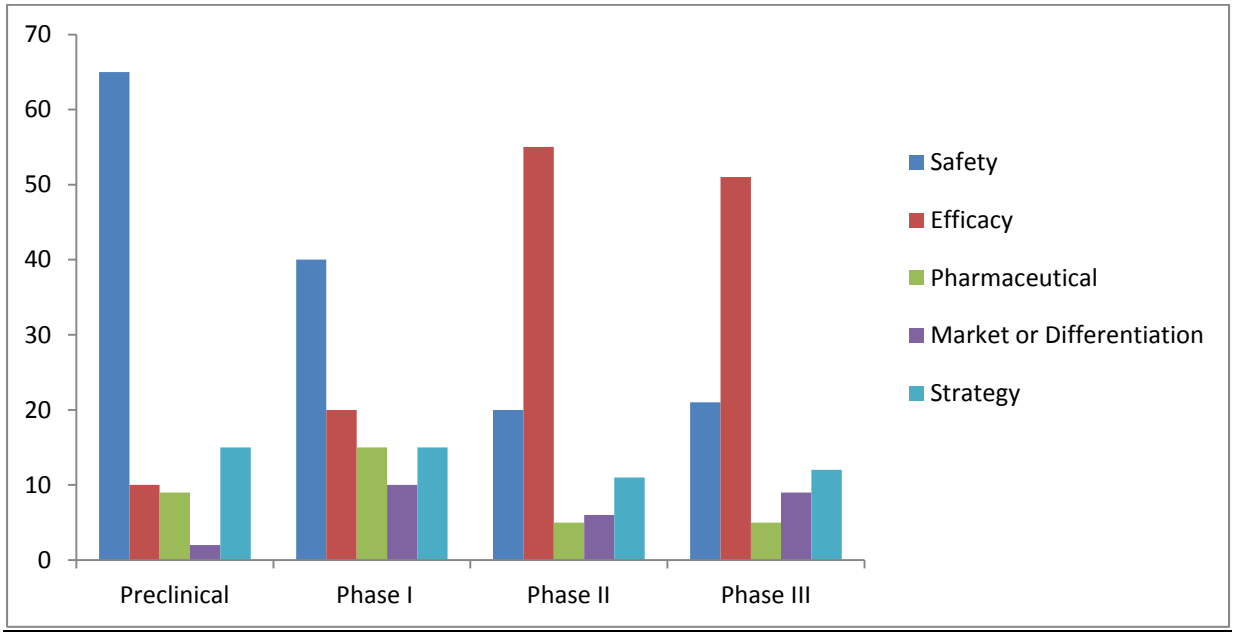

Figure 2: Reasons for attrition

Significant roadblocks may be encountered during clinical trials of the repositioning candidate. New phase 1 trials may be required to complete or supplement the data package for the candidate if initial clinical trials do not meet current regulatory requirements, adding cost, time and risk of regulatory disapproval. Moreover, other issues that may be encountered during clinical trials include the possibility that proof-of-concept studies in the new indication may fail, particularly if the new target is clinically unprecedented, or if serious safety concerns emerge during clinical trials.[4]

Objectives:

1. To study the Prospect of large scales *in silico* methodologies for off-target discovery with low cost and high efficiency- an approach to accelerate drug discovery.
2. To Study the current methodologies adopted.
3. To study the regulatory pathways for the approval of repurposed drugs and the rewards, challenges and incentives associated in US and EU.

The Path of Least Resistance: Repositioned Drugs

An alternative drug development strategy is exploration of drugs that have already been approved for treatment of other diseases and/or whose targets have already been discovered. The process of finding new uses of existing drugs outside the scope of the original indication is variously referred as "Repositioning, redirecting, Repurposing and Drug Reprofiling".[5]

Drug Repositioning: ways to bridge the innovation gap

Broadly, drug repositioning identifies new indications for drug/compounds which fall into the following categories:

1. Drugs in clinical development

Drugs whose mechanism of action is relevant to more than one disease entity, clinical development for the new indication and the original indication can be carried out simultaneously, that is "piggy backed"(e.g., clinical development of dulovetine, a non selective serotonin-reuptake inhibitor was simultaneously carried out for depression and stress urinary incontinence).

Drugs that failed to demonstrate efficacy for a particular indication during phase II and III clinical trials but which have no major safety concerns.

It is estimated that any given point of time, more than 2000 compounds are lying idle at major pharmaceutical companies after failing phase II or III trials, and the industry shelves a further 150 to 200 compounds every year, of which 50% of stalled phase II drug candidates are discounted due to efficacy

2. Drugs that have been discontinued for commercial reasons, i.e., budgetary issues, duplicate projects, or change in portfolio strategy.
3. Marketed drugs for which patents are close to expiry or when generic versions are already available.
4. Drugs that have been discovered, developed, and marketed in emerging markets but not launched in large markets of the developed world, especially in US and Europe. This also known as geographic or transnational drug repositioning.[6]

Serependity of sildenafil citrate: Angina drug becomes erection improver: Sildenafil (a.k.a Viagra, Vitamin V, the Blue pill) UK-92480, potent inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5), an enzyme that regulates blood flow had failed. Initially arrowed to treat angina, couldn't even make its way out of preliminary clinical trials. It seemed like many other compounds, this compound could also be shelved into the freezer of big pharma. Out of the blue, the compound accounted for a rare side effect; improved erections in a number of men participating in clinical trial. Though initially it was brushed a side, later it was tested in men with erectile dysfunction and the rest is a pharmaceutical history. In 1998, the drug, renamed Viagra (Sildenafil citrate), became the first oral impotence medication approved by the U.S. Food and Drug Administration, sales account for 90% of the global market for erectile dysfunction.

*Recently discovered uses include alleviation of altitude sickness and jetlag. It is also used to treat pulmonary hypertension under the brand name Canakinumab (trade name Ilaris) a recombinant monoclonal antibody developed initially for RA. It acts by blocking an immune system protein known as interleukin – 1beta (1L -1β). It failed in phase II clinical trials as it could not reach the targeted clinical end points and thus was discontinued. Another rare disease named Muckle-Wells syndrome, which is characterized by genetically predisposed high levels of 1L -1β. Additional trials in rare diseased population have showed irrefutable results of 97% affirmed subsidence of the symptoms within hours of treatment. The U.S Food and Drug Administration (FDA) has approved and given orphan drug status to the drug for two forms of cryopyrin associated periodic syndrome (CAPS): Muckle Wells and familial cold auto inflammatory syndrome. It has also received priority approval in the EU. Novartis is now conducting trials to unlock more doors by the drug to treat other inflammatory indications such as Chronic Obstructive Pulmonary Disease (COPD), gout, RA, osteoarthritis (OA), and Vacuities in stratified groups of patients whose disease is highly dependant on 1L -1β overproduction.

Pain reliever-stroke preventive:

And then there's aspirin: originally created to treat pain, it's now taken by millions to reduce the risk of heart attack and stroke.

So far, despite various repositioning initiatives, only a few drugs have been successfully approved for new indications. Nevertheless, there is considerable interest in drug repositioning and many potential candidates have been investigated for newer indications.[7]

Table 1: Existing drugs successfully repositioned for new indications:

S. No	Drug	Original indication	New indication
1.	Amantadine	Influenza	Parkinson's disease
2.	Amphotericin	Fungal Infections	Leishmaniasis
3.	Aspirin	Inflammation, Pain	Antiplatelet
4.	Atomoxetine	Antidepressant	Attention deficit hyperactivity disorder
5.	Bromocriptine	Parkinson's disease	Diabetes mellitus
6.	Colchicine	Gout	Recurrent pericarditis
7.	Gabapentin	Epilepsy	Neuropathic pain
8.	Methotrexate	Cancer	Visceral Leishmaniasis, rheumatoid arthritis and other autoimmune disorders
9.	Propranolol	Hypertension	Migraine prophylaxis
10.	Retinoic acid	Acne	Acute promoyelocytic leukaemia
11.	Zidovudine	Cancer	HIV/AIDS
12.	Raloxifin	Osteoporosis	Breast cancer
13.	Thalidomide	Morning sickness	Multiple myeloma, leprosy
14.	Milnacipran	Antidepressant	Fibromyalgia

Table 2: Potential drug candidate evaluated for new indications:

S.no	Drug	Original indication	Potential use
1.	Auranofin	Rheumatoid arthritis	Malaria
2.	Bimatoprost	Glaucoma	Promoting eye lashes
3.	Ceftriaxone	Bacterial infections	Amyotrophic lateral sclerosis
4.	Closantel	Liver fluke infection in cattle and sheep	River blindness: *Onchocerca volvulus* infection
5.	Dapsone	Leprosy	Malaria
6.	Disulfiram	Alcoholism	Melanoma
7.	Eflornithine	African trypanosomiasis	Hirsutism
8.	Fluphenazine	Antipsychotic	Multiple myeloma
9.	Minocycline	Bacterial infections	Amyotrophic lateral sclerosis
10.	Naproxen	Inflammation, pain	Prevention of Alzheimer's disease
11.	Nortriptyline	Depression	Neuropathic pain
12.	Itraconazole	Fungal infections	Cancer
13.	Astemizole	Allergic rhinitis	Malaria
14.	Quinacrine	Malaria	Prion diseases

ACCELERATING DRUG DISCOVERY THROUGH TECHNOLOGY

Involution of human genome sequencing

Out of 4500 disorders with the known molecular basics only 250 of them have exact treatments available till today, with a yawning gap between the basic knowledge and the application of basic knowledge presenting a challenge for the drug discovery. One way to make the process of drug discovery faster is the utilization of technology in every possible way. The cost of human genome sequencing which was $100M also has rapidly fallen in the past decade to $ 10,000 making it available for the researches in unzipping the human instruction book with letters ACGT. Every additional genomic piece of information is important in the sense that each new gene or function is a potential drug target.

***In silico* approaches: Knowledge based drug repositioning**

Ideas for repositioning can come from serendipitous observations, from informed insights, or from novel platforms established to identify repositioning opportunities. Bioinformatics and data mining can be used for identification of potential targets and repositioning candidates. Rapid advances in genomic, proteomic, structural, functional, and system studies of the known targets and other disease proteins have enabled the discovery of drugs, multi target agents, combination therapies, and analysis of on-target and off-target toxicity and pharmacogenomic responses using publicly available databases loaded with information about many of the proteins found in the human body.[8]

Table 3: Publicly available databases for knowledge based drug repositioning

Publically Available Databases		
Sequence Databases	**Nucleotide databases:** International repository for all nucleotide sequences submitted by researches	**EMBL:** European Molecular Biology Laboratory, Genbank **DDBJ:** DNA Data Bank of Japan
	Protein databases: Contains translated sequences from EMBL, adaptations from PIR, extracted from the literature and directly submitted by researches. Data is cross referenced to other databases	**Swiss Prot:** Swiss Protein **TrEMBL:** Translated EMBL **PIR:** Protein Information source **Ref Seq P:** Reference Sequence Proteins
Bibilographic databases	For all medically related papers	PubMed from NCBI
Clinical databases	Registers known as mutations in the human genome and the disease they cause	Human Gene Mutation Database, cardiff, UK DbSNP, Bethesda, USA: Largest single nucleotide sequence polymorphs database
World Drug Index	Authoritative index for marketed and development drugs created by Thomson Reuters.	With internationally-recognized drug names, synonyms, trade names, trivial names and trial preparation codes in one source, plus compound structures and activity data, it is ideal for finding

	chemical information relating to drug research and marketing queries.

Crowd Sourcing Drug Development

Could pharma open its drug freezers? This is the article sited immature when it revealed that about 30,000 drugs have been shelved by the pharmaceutical industry over the past three decades by various reasons of failures during the drug development. The reason could be either lack of efficacy after phase I or the company might have moved out of a given therapeutic area**.**

NIH's National Centre for advanced Translational Sciences (NCATS) launched a pilot programme "Discovering New Therapeutic Uses for Existing Molecules" in May 2012 inviting researches to look for new uses for 58 abandoned compounds contributed by eight big drug companies. All the 58 compounds were taken through preclinical testing and into early human trials at a cost of millions of dollars, and all were found to be safe.[9]

Big Pharmaceutical company perspective

Most large drug companies pursue some sort of drug repositioning activity, either formal or ad hoc. Those that have dedicated resources to repurposing include

- The new indications discovery unit at the Novartis Institute for Biomedical sciences
- Bayer Healthcare's Common mechanism research
- Pfizer's indications discovery Unit (IDU)

REGULATORY SCOPE

LEGAL FRAMEWORK IN THE U.S AND EU

PROVISIONS OF THE FOOD AND DRUG, AND COSMETIC ACT AND THE CODE OF FEDERAL REGULATIONS

New Drug Applications

In the U.S., section 505, chapter V of the Federal Food, Drug and Cosmetic Act (FD&C) lays down the requirements that need to be met by the applicant and the secretary (i.e FDA) for new drug applications (NDA). While subsection (b) (1) lays down the requirements for full dossier NDA's, NDA's submitted under subsection (b) (2) are explicitly allowed to use studies, for which the applicant has not obtained a right of reference or use. Such studies shall be defined as "non-proprietary" hereafter.

"An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant were not obtained a right of

reference or use from the person by or for whom the investigations were conducted shall also include-

(A) A certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (C)

1. That such patent information has not been filed,
2. That such patent has expired
3. Of the date on which such patent will expire, or
4. That such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(B) If with respect to the drug for which investigations described in paragraph (1) (A) were conducted information was filed under paragraph (1) or subsection (C) for a method of use of patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use."

Clause (A) requests applicants to file a certification that patent rights are not infringed by the manufacturers, use or sale of the drug. Clause (B) requires applicants to submit a statement that method of use patents will not be infringed if such patents were submitted with the original investigations, on which the applicant chooses to rely. Such certifications of non infringement also have to be sent to each owner of the patent that is the subject of the certifications as well as the marketing authorization holder of the drug substance that is the subject of the certifications.

Note that section 505(b) (2) of the FD&C Act does not specify the source from which the investigations "not conducted by or for the applicant and for which the applicant has obtained a right of reference or use" can be used. In fact, any published study can be referenced to support a 505 (b) (2).

Application had a Reference Listed Drug (RLD) is not needed so that even applications for NMEs can be approved under the provisions of this subsection so long as they rely on non-proprietary studies. For applications that rely on RLD's, the code of Federal Regulations (CFR) further specifies the requirements for such applications:

"The act does not permit approval of an abbreviated new drug application for a new indication, nor does it permit approval of other changes in a listed drug if investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the change. Any person seeking approval of a drug product that represents a modification of a listed drug (e.g., a new indication or new dosage form) and for which investigations, other than bioavailability or bioequivalence studies, are

essential to the approval of the changes may, except as provided in paragraph (b) of this section, submit a 505 (b) (2) application. This application need contain only that information needed to support the modification(s) of the listed drug."

Thus any application that relies on a RLD and that contains studies beyond the sole demonstration of bioavailability or bioequivalence must be submitted under the section 505 (b) (2) of the FD&C Act. Such applications may not be submitted as Abbreviated New Drug Application (ANDA) typically used for generics. Situations may occur where the BE of a generic drug falls intentionally or unintentionally short of that of the RLD. Paragraph(b) rules out of those applications that may be submitted under the provisions of 505 (b) (2) in these situations.[10]

Biologics License Applications

Of importance in this context is the question whether regulations similar to section 505 (b) (2) of the FD&C act exist for biologics, which usually get licensed through BLA's

(Biologics License Applications). The Public Health Service Act (PHSA) gives clarity as follows.

"The Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 seq.) applies to a biological product subject to regulation under this section, except that a product for which a license has been approved under subsection (a) shall not be required to have an approved application under section 505 of such Act 21U.S.C. 355)."

REQUIREMENT FOR PAEDIATRIC STUDIES

Since the Paediatric Research Equity Act (PREA) came into force in 2007, the CFR and the FD&C Act require that 505 (b) (2) applications contain paediatric data.

Exclusivity and Incentives Granted by the FDA for Drugs, Paediatric studies and orphans Approved under the provisions of section 505 (b) (2) of the FD&C Act

505(b) (2) applications for previously approved drugs are rewarded with a 3-year market exclusivity term if they contain studies other than BE studies. "If an application submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b), is approved after the date of the enactment of this clause (enacted sept. 24, 1984) and if such application contains reports of new clinical investigations essential to the approval of the application and conducted or sponsored by the applicant, the secretary may not make the approval of an application effective before the expiration off three years from the date of the approval of the application under subsection (b) if the investigations described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the

applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted."[11-15]

PROVISIONS OF THE DIRECTIVE 2001/83/EC, THE PAEDIATRIC REGULATION EC/1901/2006 AND REGULATION EC/726/2004

Marketing Authorization Applications for Drugs

The provisions of section 505(b)(2) of the FD&C Act cover all applications that rely on non-proprietary studies ranging from NME's to generics that deviate from the RLD substantially enough to make studies that go beyond the typical demonstration of bioavailability and bioequivalence a necessity. In the EU, short of generics; the situation where applicants can rely on RLD's or non-proprietary studies is not as well defined as in the U.S. In fact EU regulations analogues to the provisions of section 505 (b)(2) of the FD&C Act are embedded within the framework for generic drugs and similar biologics; all of which are regulated by article 10 of Directive 2001/83/EC.

New drug applications for marketing authorization are usually submitted in accord with Articles 6 and 8(3) of Directive 2001/83/EC if they contain the full set of preclinical and clinical studies. RLD's or, as per EU jargon, reference medicinal products, are always drugs initially approved under the provisions of article 8(3) regardless of any follow-up lifecycle approvals within the meaning of "Global marketing Authorization" as defined by Article 6 of directive 2001/83/EC.

Marketing Authorization Applications for Biologics

As already stated regulations for approval of bio generics exist in the EU, in contrast to the U.S. "where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided."

Requirements for Paediatric studies

A striking difference between section 505 (b)(2) of the FD&C Act and Article 10(3) of Directive 2001/83/EC is that paediatric studies are not required for Article 10 submissions. The Paediatric Regulation lays down that: "Articles 7 and 8 shall not apply to products authorised under Articles 10, 10a, 13 to 16 or 16a to 16i of Directive 2001/83/EC."

Paediatric studies as defined by the Paediatric Investigation Plan (PIP) are thus only required for marketing authorization applications submitted under the provisions of Article 6 and 8(3) of Directive 2001/83/EC.

EXCLUSIVITY AND INCENTIVES GRANTED BY THE EUROPEAN COMMISSION FOR DRUGS, PAEDIATRIC STUDIES AND ORPHANS

Marketing Authorization Application filed under the provisions of Article 6 and 10(5) of Directive 2001/83/EC

Applications based on full dossiers are filed under the provisions of Articles 6 and 8(3) of Directive 2001/83/EC. They enjoy a data exclusivity period of 8 years in addition to 2 more years of market exclusivity:

Article 10(5) grants applications for well-established drugs a protection period of one year provided that approval is based on significant preclinical or clinical studies supporting the new indication.

Paediatric Development Incentives

Protection extension in return of a compliant PIP is closely tied to Supplementary Protection Certificates (SmPC's) in the EU. If a SmPC can be obtained MMAA's submitted under the provisions of Articles 6 and 8(3) of Directive 2001/83/EC can benefit patent extension based on a PIP as laid down by the Paediatric Regulation

Orphan Exclusivity

For Orphan drugs, market protection of 10 years is granted:

As orphan drugs fall to the mandatory scope of Regulation EC/726/2004, they have to be approved through the centralized procedure. Regulation EC/726/2004 permits the use of Article 10(3) of Directive 2001/83/EC for repurposed drugs or use of bibliography data in MMAA's.

DISCUSSION

The comparison between the U.S and EU regulations reveals great differences with a view to the repurposing of known drugs. In general, U.S. regulations are less clustered as section 505 (b) (2) covers applications cross-referencing RLD's and those that rely on non-proprietary studies, or a combination of both. These particulars are regulated by different sections, or a combination of both. These particulars are regulated by different sections of directive 2001/83/EC in the EU. The European counterpart of section 505 (b)(2) is Article 10(3) of Directive 2001/83/EC. Applications for well established drugs are afforded 1 year of protection only. To obtain full data protection of eight years in the EU, sponsors are thus required to submit full dossiers for drugs not well established in the community. However, these can in part rely on bibliographical data. While the incentives for paediatric developments are comparable between the U.S and EU, the EU ties these incentives to the SmPC, which will typically not be granted to repurposed drugs that used to be

approved in EU. Sponsors who develop known drugs for new indications that are also affect the paediatric population may be punished in two ways: They may not be granted the SmPC in the first place, and therefore will not be afforded the 6-month extension upon completion of paediatric studies. While the EU has put the PUMA bill in place to explicitly support the development of known drugs exclusivity for children, such support is painfully lacking for indications that carry over to adults as well. In the U.S provisions, analogues to the PUMA regulations do not exist.[16]

The results of this comparative analysis are summarized below. In addition, guidelines have been issued by the FDA, the European Commission and EMA/CHMP, summarizing some of the key issues on 505 (b) (2) and hybrid applications. As the extent to which studies conducted for a RLD can be reference or bridged, the FDA guidance recommends devising and submitting a development plan identifying studies to be cross-referenced or bridged. The FDA will review the plan and critique it as appropriate. The guidance on hybrid applications issued by the European Commission explains the definition of significant preclinical and clinical studies as required by Article 10(5) of Directive 2001/83/EC while the EMA guidance is an online Q&A document mostly handling procedural aspects of hybrid applications.[17-20]

Table 4: Drug Repurposing Regulations in the U.S and EU

	US		**EU**	
	Drugs	**Biologics**	**Drugs**	**Biologics**
Legal basis for use of cross references to RLD's	Sec 505(b)(2) of the FD&C Act	Sec 505(b)(2) of the FD&C Act for biologics of low complexity	Sec 505(b)(2) of the FD&C Act for biologics of low complexity	None
Legal basis for use of non-proprietary studies	Sec 505(b)(2) of the FD&C Act	Sec 505(b)(2) of the FD&C Act for biologics of low complexity	Annex I part II No. 7 of Dir. 2001/83/EC Annex I Part II No. 1 of Dir. 2001/83/EC	Annex I part II No. 7 of Dir. 2001/83/EC Annex I Part II No. 1 of Dir. 2001/83/EC
Paediatric development Plan	Required	Required	Not Required for Art. 10(3) submissions	Required
Paediatric Use Marketing Authorization	N/A	N/A	Yes	Yes
Data Exclusivity	3 years/5 years for NME's	3 years/5 years for NME's	1 year for well established drugs 8 years for full dossiers as per Art 6 of Dir. 2001/83/EC	1 year for well established drugs 8 years for full dossiers as per Art 6 of Dir. 2001/83/EC
Incentives for Paediatric studies	6-month exclusivity	6-month exclusivity	6-month SmPC extension	6-month SmPC extension

	extension	extension	10-year market protection for PUM	10-year market protection for PUM
Incentives for Orphan drugs	7-year market protection	7-year market protection	10-year market protection	10-year market protection
Combined Orphan/Paediatric Incentives	7-year and 6-year market protection	7-year and 6-year market protection	12-year market protection	12-year market protection

SUMMARY AND CONCLUSION

Its highly convincing for the pharmaceutical drug development to imagine and hit the trajectory of Moore's law but its evident that by the use of technological, managerial and scientific advances it can override the Eroom's law; a little light at the end of the tunnel. Drug repurposing could be one of the multiple answers to the questions unanswered in the eternal position of drug discovery. Chronicles tell us that drug repurposing has a long history, though dominated by Serependity and the concept increases the value of the unvalued and once disposed positing change in the narrow clinical research strategy. It's high time to apply the know-how and resurrect the every possible chance to unleash many hidden cures for much waiting wonders to happen. Systematically engineered, it many answer both wealth for the pharmaceutical industry and panacea for the diseased. With the advent of new tools facilitating drug developers to screen approved compounds for new treatments, the repurposing of known drugs should become a steady pillar in every R&D department. In this work, current U.S and EU regulations are reviewed, compared and assessed for their effectiveness. A regulatory strategy highlighting the importance of freedom to operate and early health technology assessment is proposed. When compared to the U.S., EU regulations are less supportive, more restrictive and under certain circumstances even futile. As the development of known drugs in new therapeutic areas can provide much benefit to industry, public healthcare players, European legislators should increase their efforts to facilitate such developments.

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