Regulatory Strategy for the Development of Known Drugs in New Therapeutic Areas

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List of Abbreviations

ADHD .....Attention Deficit / Hyperactivity Disorder
ANDA .....Abbreviated New Drug Application
BLA .....Biologics License Application
BPCA .....Best Pharmaceuticals for Children Act
C .....Cost
CFR.....Code of Federal Regulations
CHMP.....Committee for Medicinal Products for Human Use
CT .....Cycle Time
CoTA.....Continuous Technology Assessment
EMA .....European Medicines Agency
FD&C Act .....Food, Drugs, and Cosmetics Act
FOI .....Freedom of Information
GRH .....Gonadotropin-Releasing Hormone
HTA.....Health Technology Assessment
HTS.....High-Throughput Screening
MAA .....Marketing Authorization Application
MAH .....Marketing Authorization Holder
MMAA .....Mixed Marketing Authorization Application
MS.....Multiple Sclerosis
N/A .....Not Available or Not Applicable
NDA .....New Drug Application
NIH.....National Institutes of Health
NME .....New Molecular Entity
Non-proprietary studies .....Studies 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
NPC .....NCGC Pharmaceutical Collection
P.....R&D Productivity
PAR.....Public Assessment Report
PHSA .....Public Health Service Act
PIP .....Pediatric Investigation Plan
PREA .....Pediatric Research Equity Act
PTE .....Patent Term Extension
PTS .....Probability of Technical Success
PUMA.....Pediatric Use Marketing Authorization

RBA.....Risk Benefit Assessment
RBB.....Risk Benefit Balance
RLD.....Reference Listed Drug
SmPC.....Summary of Product Characteristics
SPC.....Supplementary Protection Certificate
TPP .....Target Product Profile
UMN.....Unmet Medical Need
USC .....United States Code
V.....Value
WIP .....Work In Process

1 Introduction

Over the past 10 years, the business model of the pharmaceutical industry has been challenged by increased regulatory scrutiny due to serious concerns about the industry's transparency and integrity.[1,2] As a result, the industry's price/earnings ratio has decreased below that of the S&P 500 index and has remained shallow, as have share prices for the past 7 years.[3] Secondly, the industry has also been put to much pressure by generics and increasing health care budget constraints. In the U.S., generics account for 70% of all prescriptions.[4] In Europe, a fourth hurdle has been introduced in key countries where, after approval, new drugs are evaluated for their cost/benefit balance compared to existing therapies by such institutes as IQWIG (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*) in Germany.[5] Furthermore, the pharmaceutical industry is being confronted with decreased R&D productivity and a dramatic loss of annual sales due to important patent expirations between 2010 and 2014, which has been forecast to be $113 billion, and for which each dollar lost is predicted to be replaced by only 26 cents with new product launches.[6-7] Indeed, experienced observers and industry analysts have even gone so far as to predict the industry's downfall in light of this unprecedented combination of adverse developments.[8-10]

With the current average capitalized cost of $1.8 billion and the average time of 13.5 years for the development of a first-in-class NME (New Molecular Entity) it is clear that R&D productivity has to improve dramatically to counteract the detrimental trends delineated above.[11] 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 process (WIP), probability of technical success (PTS), value (V) in the nominator and cycle time (CT) and investment costs C in the denominator, R&D productivity (P) can be described as

$$P = \frac{WIPxPTSxV}{CTxC}$$

in adaptation of the pharmaceutical value equation.[3] 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 view 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 (62% attrition rate in phase II and 45% in phase III).[12] The combined success rate of phase III and approval has even fallen to 50% in recent years.[13] Interestingly, these failures

could generally be avoided if more time was spent on target validation and proof-of-concept studies using appropriate animal models and human volunteers in phase I and II, rather than prematurely advancing into phase III. In fact, as Steven Paul *et al.* point out, phase III clinical trials should only fail because of unexpected adverse drug reactions and not because of poor portfolio management and short-term business imperatives.[3]

In addition to these introductory considerations, strategies beyond the classic understanding of innovative drug development (i.e. the development of NME's working through new mechanisms of action) exist that have proven to reduce development costs and risks. They have worked without having to substantially increase WIP to compensate for the risky, cost- and time-intensive endeavor of creating first-in-class NME's. Most notably, the "me too" approach to develop modified NME's acting on proven targets, for which approved yet similar drugs exist, has been widely used. This approach effectively increases R&D productivity through increasing WIP, PTS, V and decreasing CT and C, as AstraZeneca's Nexium has powerfully demonstrated to name but one example. The FDA approved Nexium in 2001 after patent protection expired for Nexium's predecessor Prilosec. While Prilosec was a racemic mixture of the drug substance, Nexium only contained the L-isomer effectively extending patent protection while offering no convincingly proven additional benefit.[14] As me-too drugs have often shown little benefit over existing therapies, this approach towards boosting R&D productivity has been the subject of extensive debate.[1,15] In times of limited public health budgets, policy makers and healthcare payers are no longer willing to reimburse the pharmaceutical industry for medicines that show little benefit over existing and more cost-effective therapies. As a result, today's industry is facing the extraordinary challenge to meet the demands from both regulatory agencies and third party payers.[16]

A more sustainable approach to increase R&D productivity is by repurposing approved or once approved drugs for new therapies. The novelty and cost effectiveness of this approach become immediately obvious when a qualified drug with a well-known safety profile is discovered to be effective in new therapeutic areas. The most famous example is probably Thalidomide, which was used as a sedative and as a treatment for morning sickness during pregnancy in the 1950's. Creating severe birth defects, it was withdrawn and decades later reapproved by the FDA for the treatment of leprosy in 1998 and multiple myeloma in 2006.[17,18] As such, Thalidomide has served as an inspiring example of improving R&D productivity through finding new uses for old drugs. A second, less famous albeit not less creative example is Bimatroprost, which is a prostaglandin analogue originally approved for the reduction of intraocular pressure by the FDA in 2001. Growth of eyelashes is a common side effect for this treatment so it was not surprising when a new NDA for this cosmetic indication was approved by the FDA in 2008.[19] The advantage of using established drugs is

obvious. They have been found to be safe and efficacious in their original indication, they usually have beneficial pharmacokinetic properties and in cases where a large human safety database exists they can enter human testing sooner than first-in-class NME's. Developing approved drugs for new indications therefore increases PTS and decreases CT and C, resulting in the substantial improvement of P. One could argue that V is less for repurposing known drugs when compared to the creation of a first-in-class NME as follow-up developers cannot file patent applications claiming the molecule, and exclusivity terms are often shorter, too. This however does not per se affect patent protection of the new indication and may be offset by the overall improvements of PTS, CT and C. As such, Thalidomide has become the flagship product for Celgene and further examples exist where repurposing old drugs has added impressive value to companies' portfolios.[20]

Still, it appears the full potential of this lower risk and lower cost approach has not yet been realized by the pharmaceutical industry.[21] NIH (National Institutes of Health) researchers have recently compiled a comprehensive database of all approved molecular entities. The NCGC Pharmaceutical Collection (NPC) browser was created with a view to rare and neglected diseases, but it shows much promise for identifying candidates in lead indications as well.[22] Amongst investigational drugs, biologics and drugs for veterinary use, the database contains over 4500 compounds approved by the FDA, and 2700 compounds approved by all key health authorities (FDA, EMA, Canadian and Japanese authorities) for clinical use (Fig. 1).[23] Information can be searched by compound structure, synonyms, approved indications and mode of action. Data on known human targets, current clinical trials and known diseases including rare and neglected ones are provided and can be searched as well. In addition, the NPC database is capable of providing solutions to specific problems. For example, a search can be done for all kinase inhibitors listed in the FDA orange book or for compound structures used in clinical trials. This database offers a comprehensive and user-friendly set of tools that ought to be very useful for the HTS stage of drug development.

NPC informatics (14,814)
NPC screening (3,272)
Approved drugs (7,929)
Human approved drugs (7,793)
FDA approved (4,655)
FDA human approved (4,464)
Structure undefined (5,681)
Biologics (807)
Inorganics (531)
HTS amenable drugs (7,630)
FDA drugs@FDA (1,750)
FDA orange book (1,661)
FDA NDC (3,358)
FDA OTC (1,088)
FDA DailyMed (1,176)
FDA green book (426)
US DEA (282)
Canada (2,673)
UK NHS (1,707)
Japan (2,345)
EMA human approved (325)
EMA veterinary approved (33)

Fig. 1 List of pharmaceuticals implemented in the NBC database (from http://tripod.nih.gov/npc)

This thesis dissects the regulatory framework in the U.S. and Europe for the development of known drugs in new therapeutic areas by follow-up developers. The regulatory environment is compared between the two

regions with a view to important strategic issues such as patent protection, data exclusivity and health technology assessment. In support of this analysis, databases were searched for repurposed drugs successfully filed and approved. Based on these findings, a regulatory strategy for the repurposing of drugs is proposed.

2 Legal Framework in the U.S. and EU

2.1 Provisions of the Food, Drug, and Cosmetic Act and the Code of Federal Regulations

2.1.1 New Drug Applications

In the U.S., Section 505, Chapter V of the Federal Food, Drug, and Cosmetic Act (FD&C Act) lays down the requirements that need to be met by the applicant and the secretary (i.e. FDA) for new drug applications (NDA's). 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 has 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 the drug for which such investigations were conducted or 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)—*
>
> *(i) that such patent information has not been filed,*
>
> *(ii) that such patent has expired,*
>
> *(iii) of the date on which such patent will expire, or*
>
> *(iv) 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 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."* [a]

Clause (A) requests applicants to file a certification that patent rights are not infringed by the manufacture, 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-

[a] Section 505(b)(2) of the FD&C Act

infringement also have to be sent to each owner of the patent that is the subject of the certification as well as the marketing authorization holder of the drug substance that is the subject of the certification:

> *"Notice of certification. For each patent which claims […] a use for such drug or drugs and which the applicant certifies under 314.50(i)(1)(i)(A)(4) that a patent is invalid, unenforceable, or will not be infringed, the applicant shall send notice of such certification by registered or certified mail, return receipt requested to each of the following persons:*
>
> *(1) Each owner of the patent that is the subject of the […] and*
>
> *(2) The holder of the approved application under section 505(b) of the act for each drug product which is claimed by the patent or a use of which is claimed by the patent and for which the applicant is seeking approval […]."* [a]

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 not 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 and 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."* [b]

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

> *"An application may not be submitted under this section for a drug product whose only difference from the reference listed drug is that:*
>
> *(1) The extent to which its active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug; or*

[a] 21 CFR 314.52(a)
[b] 21 CFR 314.54(a)

> *(2) The rate at which its active ingredient(s) is absorbed or otherwise made available to the site of action is unintentionally less than that of the reference listed drug."* [a]

505(b)(2) applications relying on RLD's are particularly attractive as they only need to contain the information supporting changes from the RLD such as a new indication. The CFR rules that only amendments and supplements can be submitted on the basis of a reduced data package, too:

> *"An application for a new chemical entity will generally contain an application form, an index, a summary, five or six technical sections, case report tabulations of patient data, case report forms, drug samples, and labeling, including, if applicable, any Medication Guide required under part 208 of this chapter. Other applications will generally contain only some of those items, and information will be limited to that needed to support the particular submission. These include an application of the type described in section 505(b)(2) of the act, an amendment, and a supplement."* [b]

2.1.2 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 et 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 (21 U.S.C. 355)."* [c]

This means that while the FD&C Act also applies to biologics, they are not approved as per the requirements of section 505 of this act. In fact, there is no mechanism in place that allows applicants to rely on licensed biologics, which the FDA has already found to be safe and efficacious. Likewise, the PHSA does not contain a section similar to Section 505(j) of the FD&C Act for generics, which would provide a regulatory route for biosimilars analogous to EU regulations. An important exception are biologics of low to intermediate complexity, which are usually not glycosylated and therefore not a priori considered unsafe due to immunogenicity concerns. Quite a few therapeutic peptides such as somatostatin and gonadotropin releasing hormone as well as larger proteins such as glucagon and insulin fall to the category of biologics approved via NDA's. For these medications, 505(b)(2) applications and even ANDA's have been approved by the FDA.[24]

2.1.3 Requirement for Pediatric Studies

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

[a] 21 CFR 314.54(b)
[b] 21 CFR 314.50
[c] Section 351(j) of the PHS Act

> *"Required assessment. Except as provided in paragraphs (b), (c), and (d) of this section, each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective."* [a]

> *"New drugs and biological products.*
>
> *(1) In general. A person that submits, on or after the date of the enactment of the Pediatric Research Equity Act of 2007 [enacted Sept. 27, 2007], an application (or supplement to an application)—*
>
> *(A) under section 505 for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, or*
>
> *(B) under section 351 of the Public Health Service Act (42 USC 262) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall submit with the application the assessments described in paragraph (2)."* [b]

Thus, any drug or biologics application for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration must contain the pediatric research assessment as per paragraph (2) of this section, which lays down the particulars of such assessment including deferrals, waivers and labeling requirements. Surprisingly, holders of 505(b)(2) marketing approvals appear to be exempt from written requests by the FDA to conduct pediatric studies as these are generally only issued to sponsors of clinical trials, sponsors of 505(b)(1) applications or holders of approved 505(b)(1) marketing approvals.

> *"Request for studies.*
>
> *(A) In general, the Secretary may, after consultation with the sponsor of an application for an investigational new drug under section 505(i); the sponsor of an application for a new drug under section 505(b)(1); or the holder of an approved application for a drug under section 505(b)(1), issue to the sponsor or holder a written request for the conduct of pediatric studies for such drug."* [c]

Note that orphan drug applications are exempt from the requirement to contain pediatric data regardless of whether the application is filed under Section 505(b)(1) or 505(b)(2) of the FD&C Act.

> *"Exemption for orphan drugs. This section does not apply to any drug for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter."* [d]

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[a] 21 CFR 314.55(a)
[b] Section 505B(a)
[c] Section 505A(d)(1)(A)
[d] 21 CFR 314.55(d)

2.2 Exclusivity and Incentives Granted by the FDA for Drugs, Pediatric Studies and Orphans Approved under the Provisions of Section 505(b)(2) of the FD&C Act

2.2.1 New Drug Applications Submitted under 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 bioequivalence 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 (other than bioavailability studies) 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 of 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."* [a]

The CFR clarifies that this protection period is only effective against against follow-on 505(b)(2) applications and ANDA's (which would be submitted under Section 505(j)):

> *"If an application:*
>
> *(i) Was submitted under section 505(b) of the act;*
>
> *(ii) Was approved after September 24, 1984;*
>
> *(iii) Was for a drug product that contains an active moiety that has been previously approved in another application under section 505(b) of the act; and*
>
> *(iv) Contained reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the application, the agency will not make effective for a period of 3 years after the date of approval of the application the approval of a 505(b)(2) application or an abbreviated new drug application for the conditions of approval of the original application, or an abbreviated new drug application submitted pursuant to an approved petition under section 505(j)(2)(C) of the act that relies on the information supporting the conditions of approval of an original new drug application."* [b]

To be entitled to this exclusivity period, the application must have been approved after the Drug Price Competition and Patent Term Restoration Act (more commonly known as the Hatch-Waxman Act) came into force on September 24, 1984.[25] Protection is also extended to ANDA's filed under the provisions of section 505(j)(2)(C), which affords applicants to submit a petition to the FDA for use of section 505(j) for drugs that contain different active ingredients, different routes of administration, different dosage forms or different strengths.

[a] Section 505(c)(3)(E)(iii) of the FD&C Act

[b] 21 CFR 314.108(b)(4)

As these changes almost always require new investigations and submission under 505(b)(2) of the act, 505 (j)(2)(C) is seldom used and not further reviewed in this thesis.

As stated previously (compare chapter 2.1.1), NME's can theoretically also be approved under the provisions of Section 505(b)(2) of the Act. In these cases, the applicant may be granted 5 years of exclusivity:

> *"If an application submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), is approved after the date of the enactment of this clause [enacted Sept. 24, 1984], no application which refers to the drug for which the subsection (b) application was submitted and for which 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 for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted may be submitted under subsection (b) before the expiration of five years from the date of the approval of the application under subsection (b)[…]"* [a]

Note that the FD&C Act does not discriminate between applications for NME's filed under Section 505(b)(1) or 505(b)(2). The pertinent section in the CFR again clarifies this :

> *"If a drug product that contains a new chemical entity was approved after September 24, 1984, in an application submitted under section 505(b) of the act, no person may submit a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act for a drug product that contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved new drug application, [...]"* [b]

The FD&C Act also does not include protection against subsequent 505(b)(1) applications containing full dossiers. Therefore, this protection is largely based on data exclusivity rather than true market exclusivity.

2.2.2 Pediatric Development Incentives

505(b)(2) applications may benefit from pediatric exclusivity as established by the BPCA (Best Pharmaceuticals for Children Act) in 2002. Section 505A states that an additional 6-month protection period is granted to applications containing NME's or known active ingredients, resulting in 5-year and 6-month or 3-year and 6-month protection terms, respectively.

> *"(I) the period referred to in subsection (c)(3)(E)(ii) of section 505, and in subsection (j)(5)(F)(ii) of such section, is deemed to be five years and six months rather than five years, […]; or*
>
> *(II) the period referred to in clauses (iii) and (iv) of subsection (c)(3)(E) of such section, and in clauses (iii) and (iv) of subsection (j)(5)(F) of such section, is deemed to be three years and six months rather than three years; and [...]"* [c]

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[a] Section 505(c)(3)(E)(ii) of the FD&C Act
[b] 21 CFR 314.108(b)(2)
[c] Section 505A(b)(1)(A)(i) of the FD&C Act

However, if the assessment of the pediatric studies is completed later than 9 months prior to the expiration of the regular exclusivity period, an extension cannot be granted.

> *"Exception. The Secretary shall not extend the period referred to in paragraph (1)(A) or (1)(B) if the determination made under subsection (d)(3) [Meeting pediatric studies requirement] is made later than 9 months prior to the expiration of such period."* [a]

2.2.3 Orphan Exclusivity

In addition to pediatric exclusivity, 505(b)(2) applications for drugs, which have successfully been designated as orphan drugs by the FDA, are entitled to orphan drug exclusivity of 7 years regardless of whether the application was filed under 505(b)(1) or 505(b)(2):

> *"Except as provided in subsection (b), if the Secretary—*
>
> *(1) approves an application filed pursuant to section 505, or*
>
> *(2) issues a license under section 351 of the Public Health Service Act for a drug designated under section 526 for a rare disease or condition, the Secretary may not approve another application under section 505 or issue another license under section 351 of the Public Health Service Act for such drug for such disease or condition for a person who is not the holder of such approved application, of or of such license until the expiration of seven years from the date of the approval of the approved application, or the issuance of the license."* [b]

In contrast to the data exclusivity terms laid down for regular submissions (compare chapter 2.2.1), this protection is not limited to subsequent submissions that rely on the approved application. It affects all applications for the approved condition and is therefore more effective as it provides true market protection.

New and already marketed drugs successfully developed for a rare disease including the pediatric population would benefit from a 7-year and 6-month protection period as per section 505A of the Act:

> *"if the drug is designated […] for a rare disease or condition, the period referred to in section 527(a) is deemed to be seven years and six months rather than seven years [...]"* [c]

2.3 Provisions of Directive 2001/83/EC (as amended), the Pediatric Regulation EC/1901/2006 (as amended) and Regulation EC/726/2004

2.3.1 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

[a] Section 505A(b)(2) of the FD&C Act
[b] Section 527(a) of the FD&C Act
[c] Section 505A(b)(1)(A)(ii) of the FD&C Act

rely on RLD's or non-proprietary studies is not as well defined as in the U.S. In fact, EU regulations analogous 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 life cycle approvals within the meaning of "Global Marketing Authorization" as defined by Article 6 of Directive 2001/83/EC:

> *"When a medicinal product has been granted an initial marketing authorisation in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisationin accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10(1)."*[a]

Reference medicinal products are, accordingly, defined as:

> *"(a) 'reference medicinal product' shall mean a medicinal product authorised under Article 6, in accordance with the provisions of Article 8; [...]"* [b]

Note that Article 6 does not mention new indications as part of the global marketing authorization. Therefore, even drugs that were previously approved under the provisions of Article 6 for different indications, the same drugs can again be approved under these provisions for new indications. For the new indication they would be reference medicinal product again, too.

Article 10(3) lays down the requirements for applications containing deviations from RLD's beyond those allowed for typical generics (so-called hybrid applications):

> *"In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2 (b) or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided."* [c]

In contrast to section 505(b)(2) of the FD&C act, which focuses on the use of non-proprietary studies in support of any part of the application, hybrid applications as per Article 10(3) concern generic drugs that require studies tailored to the differences from the RLD's. Article

[a] Article 6 of Directive 2001/83/EC as amended
[b] Article 10(2)(a) of Directive 2001/83/EC as amended
[c] Article 10(3) of Directive 2001/83/EC as amended

10(3) does not provide a legal basis for the use of non-proprietary studies. Another important difference to Section 505(b)(2) of the FD&C Act is that Article 10(3) cannot be used for NME's as, by definition, only changes from the RLD apply. Notwithstanding these juridical differences, Article 10(3) does theoretically provide a legal basis for repurposing known drugs on the basis of an incomplete dossier because changes from the RLD's indication are explicitly included.

Article 10(5) of Directive 2001/83/EC also provides a legal basis for the repurposing of drugs:

> *"In addition to the provisions laid down in paragraph 1, where an application is made for a new indication for a well-established substance, […]."* [a]

In the EU, well-established substance is defined as:

> *"Factors which have to be taken into account in order to establish a well-established medicinal use of constituents of medicinal products are:*
>
> *— the time over which a substance has been used,*
>
> *— quantitative aspects of the use of the substance,*
>
> *— the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and*
>
> *— the coherence of scientific assessments.*
>
> *[…] In any case, however, the period of time required for establishing a well established medicinal use of a constituent of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community."* [b]

Applications for well-established drugs must contain full dossiers, which can in part rely on bibliographical data:

> *"The documentation submitted by the applicant should cover all aspects of the safety and/or efficacy assessment […] All documentation, both favourable and unfavourable, must be communicated."* [c]

Applications using non-proprietary studies are also defined in Annex I to Directive 2001/83/EC, which describes the contents of Mixed Marketing Authorization Applications (MMAA's):

> *"Mixed marketing-authorisation applications shall mean marketing authorisation application dossiers where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references. All other Module(s) are in accordance with the structure described in Part I of this Annex. The competent authority shall accept the proposed format presented by the applicant on a case by case basis."* [d]

---

[a] Article 10(5) of Directive 2001/83/EC as amended
[b] Annex I Part II No. 1(a) of Directive 2001/83/EC as amended
[c] Annex I Part II No. 1(b) of Directive 2001/83/EC as amended
[d] Annex I Part II No. 7 of Directive 2001/83/EC as amended

Accordingly, any application relying on both own and bibliographical data is by definition a MMAA and requires submission of a full dossier as per Article 8(3). As cross-references to approved drugs are not included in either regulation, approval on the basis of a reduced data package in analogy to Article 10(3) and 505(b)(2) is not possible.

2.3.2 Marketing Authorization Applications for Biologics

As already stated (compare chapter 2.1.2), regulations for approval of biogenerics (biosimilars) 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."* [a]

Note that Article 10(4) does not mention new indications, new pharmaceutical forms or new routes of administration. This section must therefore be read with a view to the fact that the purity, potency and immunogenicity of biologics heavily depend on manufacturing processes. Therefore, "appropriate" preclinical and clinical studies refer solely to the preclinical and, particularly, clinical significance of changes in the manufacture of the biogeneric when compared to the reference biologic. This section may not be used for the repurposing of biologics, unfortunately.[26] Applications for known biologics that are not biosimilars are stand-alone applications filed under the provisions of Article 8(3). To what extent such applications could be MMAA's by relying on bibliographical data such as published studies would have to be decided on a case-by-case basis.

2.3.3 Requirement for Pediatric 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 pediatric studies are not required for Article 10 submissions. The Pediatric 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."* [b]

Pediatric studies as defined by the Pediatric 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.

---

[a] Article 10(4) of Directive 2001/83/EC as amended
[b] Article 9 of Regulation EC/1901/2006 as amended

> *"An application for marketing authorisation under Article 6 of Directive 2001/83/EC […]shall be regarded as valid only if it includes, in addition to the particulars and documents referred to in Article 8(3) of Directive 2001/83/EC, one of the following:*
>
> *(a) the results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan;*
>
> *(b) a decision of the Agency granting a product-specific waiver;*
>
> *(c) a decision of the Agency granting a class waiver pursuant to Article 11;*
>
> *(d) a decision of the Agency granting a deferral."* [a]

MMAA's filed under the provisions of Articles 6 and 8(3) of Directive 2001/83/EC are therefore included. A PIP is also required for new indications, new pharmaceutical forms and new routes of administrations within an existing marketing authorization:

> *"In the case of authorised medicinal products which are protected either by a supplementary protection certificate under Regulation (EEC) No 1768/92, or by a patent which qualifies for the granting of the supplementary protection certificate, Article 7 of this Regulation shall apply to applications for authorisation of new indications, including paediatric indications, new pharmaceutical forms and new routes of administration […]."* [b]

In situations where known drugs are repurposed for the pediatric population alone, a Pediatric Use Marketing Authorization (PUMA) may be obtained under the provisions of Regulation EC/1901/2006. These provisions are particularly appealing as they do not forfeit the right to develop the same drug for other indications and *expressis verbis* allow the use of RLD's:

> *"Submission of an application for a paediatric use marketing authorisation shall in no way preclude the right to apply for a marketing authorisation for other indications.[…] Where a medicinal product is or has been authorised in a Member State or in the Community, data contained in the dossier on that product may, where appropriate, be referred to, in accordance with […] Article 10 of Directive 2001/83/EC, in an application for a paediatric use marketing authorisation."* [c]

2.4 Exclusivity and Incentives Granted by the European Commission for Drugs, Pediatric Studies and Orphans

2.4.1 Marketing Authorization Applications filed under the Provisions of Articles 6 and 10(5) of Directive 2001/83/EC (as amended)

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:

> *"By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide*

[a] Article 7(1) of Regulation EC/1901/2006 as amended
[b] Article 8 of Regulation EC/1901/2006 as amended
[c] Article 30(1-3) of Regulation EC/1901/2006 as amended

> *the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community.*
>
> *A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product."* [a]

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:

> *"In addition to the provisions laid down in paragraph 1, where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication.."* [b]

With a view to the requirements for well-established drugs (compare chapter 2.3.1) and in comparison to a minimum of 3 years of protection for 505(b)(2) applications in the U.S., the EU is quite 'stingy' on well-established drugs.

2.4.2 Pediatric 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 (compare chapter 3.2.2), MMAA's submitted under the provisions of Articles 6 and 8(3) of Directive 2001/83/EC can benefit from patent extension based on a PIP as laid down by the Pediatric Regulation:

> *"Where an application under Article 7 or 8 includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, the holder of the patent or supplementary protection certificate shall be entitled to a six-month extension of the period referred to in Articles 13(1) and 13(2) of Regulation (EEC) No 1768/92."* [c]

For PUMA's, the protection period is extended to an 8-year data exclusivity and a 10-year market protection period, which is the same as for complete submissions using Article 8(3) of Directive 2001/83/EC. No additional incentives are offered for the conduct of pediatric studies:

> *"1. Where a paediatric use marketing authorisation is granted in accordance with Articles 5 to 15 of Regulation (EC) No 726/ 2004, the data and marketing protection periods referred to in Article 14(11) of that Regulation shall apply.*
>
> *2. Where a paediatric use marketing authorisation is granted in accordance with the procedures laid down in Directive 2001/83/EC, the data and marketing protection periods referred to in Article 10(1) of that Directive shall apply."* [d]

---

[a] Article 10(1) of Directive 2001/83/EC as amended
[b] Article 10(5) of Directive 2001/83/EC as amended
[c] Article 36 of Regulation EC/1901/2006 as amended
[d] Article 38 of Regulation EC/1901/2006 as amended

Reference is made to Regulation EC/726/2004, which lays down provisions for the centralized procedure.

2.4.3 Orphan Exclusivity

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

> *"Where a marketing authorisation in respect of an orphan medicinal product is granted […], the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product."* [a]

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 bibliographical data in MMAA's as per Annex I:

> *"*Each a*pplication for the authorisation of a medicinal product for human use shall specifically and completely include the particulars and documents as referred to in Articles 8(3), 10, 10a, 10b or 11 of, and Annex I to, Directive 2001/83/EC."* [b]

As laid down by article 37 of Regulation EC/1901/2006, the 10-year protection period for orphan drugs is extended to 12 years if pediatric studies were conducted in compliance with a PIP:

> *"Where an application for a marketing authorisation is submitted in respect of a medicinal product designated as an orphan medicinal product pursuant to Regulation (EC) No 141/2000 and that application includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, [...] the ten-year period referred to in Article 8(1) of Regulation (EC) No 141/2000 shall be extended to twelve years."* [c]

Therefore, finding new therapeutic use for a know drug can result in long protection periods. However, this cannot be achieved through Article 10(3) submission, which only affords the applicant a 1-year period of data exclusivity.

2.5 Summary

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 of Directive 2001/83/EC in the EU. The European counterpart of Section 505(b)(2) is Article

[a] Article 8(1) of Regulation EC/141/2000
[b] Article 6(1) of Regulation EC/726/2004
[c] Article 37 of Regulation EC/1901/2006 as amended

10(3) of Directive 2001/83/EC. Whether or not this article has been used for new indications is a question, which will be addressed later (compare chapter 5.2). 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 pediatric 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 the EU (compare chapter 3.2.2). Sponsors who develop known drugs for new indications that are also affect the pediatric 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 pediatric studies. While the EU has put the PUMA bill in place to explicitly support the development of known drugs exclusively for children, such support is painfully lacking for indications that carry over to adults as well. In the U.S., provisions analogous to the PUMA regulations (Article 30 of Regulation EC/1901/2006) do not exist.

The results of this comparative analysis are summarized below (Table 1). 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.[27-29] As the extent to which studies conducted for a RLD can be referenced or bridged, the FDA guidance (Appendix A) recommends to devise and submit 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 (Appendix B) explains the definition of significant preclinical and clinical studies as required by Article 10(5) of Directive 2001/83/EC (compare chapter 2.4.1) while the EMA guidance is an online Q&A document mostly handling procedural aspects of hybrid applications.

Table 1: Drug Repurposing Regulations in the U.S. and EU

	U.S.		**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	Art. 10(3) of Dir. 2001/83/EC Art. 30 of Reg. EC/1901/2006	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
Pediatric development plan	Required	Required	Not required for Art. 10(3) submissions	Required

PUMA	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 biologics 8 years for full dossiers as per Art. 6 of Dir. 2001/83/EC
Incentives for pediatric studies	6-month exclusivity extension	6-month exclusivity extension	6-month SmPC extension 10-year market protection for PUMA	6-month SmPC extension 10-year market protection for PUMA
Incentives for orphan drugs	7-year market protection	7-year market protection	10-year market protection	10-year market protection
Combined orphan/pediatric incentives	7-year and 6-month market protection	7-year and 6-month market protection	12-year market protection	12-year market protection

3 Intellectual and Commercial Property Rights

In general terms, patent protection is a government-issued exclusivity right, which prevents others from using, selling or importing an invention.[30] There are three different kinds of intellectual and commercial property protection relevant to the repurposing of known drugs: Basic patents such as patents claiming new molecules with therapeutic potential and method-to-use patents (e.g. a therapeutic indication for which a drug substance appears to be effective), patent term extensions and regulatory data protection. The latter has previously been extensively reviewed (compare chapters 2.2, 2.4 and 2.5). The first two are briefly reviewed in this chapter with a view to their impact on repurposing strategies.

3.1 Basic Patents

A patent application must fulfil four main criteria to succeed and be granted 20 years of protection. The application must contain an invention, which, second, must be novel and, third, based on ingenious activities of technical nature. Last, the invention must be commercially applicable. Clearly, patents claiming NME's or novel therapeutic uses of known drugs would formally fulfil these criteria. However, new technologies used for the manufacture of drugs can be patented as well. [30,31]

One important characteristic of basic patents in pharmaceutical research is that they can be extended beyond their original expiration date to compensate the industry for lengthy regulatory review times (compare chapter 3.2). Both the U.S. and EU have similar definitions of basic patents eligible for patent term extension. The Unites States Code (USC) defines extendable patents as follows:

> *"The term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended in accordance with this section from the original expiration date of the patent […]."* [a]

In the EU, such patents are defined as:

> *"'basic patent' means a patent which protects a product as such, a process to obtain a product or an application of a product […];* [b]

Thus, method to use patents, which play a predominate role in the repurposing of known drugs, are basically eligible for extension. However, the conditions under which such patents can be extended are quite different between the U.S. and EU as delineated in the following chapter.

3.2 Patent Term Extensions

Repurposing known drugs for new therapeutic areas means that patents claiming the drug substance were filed and must have expired before the drug can be marketed for its new use. In these situations, sponsors of repurposed drugs can typically protect their invention by filing method to use patents that claim the new indication. Whether or not such patents are eligible for patent extensions depends on a number or criteria that must be fulfilled. These criteria are reviewed in this chapter.

3.2.1 U.S.: Drug Price Competition and Patent Term Restoration Act of 1984

In the US, the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch Waxman Act, amended the FD&C Act and afforded sponsors an extension of their basic patents based on FDA review times for the clinical phase (Section 505(i) of the FD&C Act lays down the provisions to conduct clinical trials) of the development program and for the approval procedure.

> *"(1) The testing phase begins on the date an exemption under section 505(i) of the Act becomes effective […] and ends on the date a marketing application under section 351 of the Public Health Service Act or section 505 of the act is initially submitted to FDA […], and*
>
> *(2) The approval phase begins on the date a marketing application under section 351 of the Public Health Service Act or section 505(b) of the Act is initially submitted to […]and ends on the date the application is approved."* [c]

On principle, method-to-use patents are eligible for patent extension as they meet the definition laid down in the USC (compare chapter 3.1). However, they must meet the following requirements to obtain an extension:

---

[a] 35 USC 156(a)
[b] Article 1(c) of Regulation EC/469/2009
[c] 21 CFR 60.22(a)

> *"(1) the term of the patent has not expired before an application is submitted […];*
>
> *(2) the term of the patent has never been extended […];*
>
> *(3) an application for extension is submitted by the owner of record of the patent or its agent and in accordance with the requirements of paragraphs (1) through (4) of subsection (d);*
>
> *(4) the product has been subject to a regulatory review period before its commercial marketing or use;*
>
> *(5)[…] the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred […];"* [a]

If a method to use patent has never been extended and has not expired, it is likely eligible for a patent term extension, which may not exceed the total patent protection of 14 years post approval.

> *"if the period remaining in the term of a patent after the date of the approval of the approved product under the provision of law under which such regulatory review occurred when added to the regulatory review period […] exceeds fourteen years, the period of extension shall be reduced so that the total of both such periods does not exceed fourteen years;"* [b]

3.2.2 EU: Supplementary Protection Certificate

In the EU, the Supplementary Protection Certificate (SmPC) is used to extend basic patents including method to use patents as per definition (compare chapter 3.1). The SmPC can on principle, extend them up to 5 years:

> *„the duration of the certificate may not exceed five years from the date on which it takes effect."* [c]

The eligibility of method to use patents for supplementary protection has been challenged before court in cases where the drug was authorized in the EU for use in a different indication.[32] Issues will also likely arise in cases where a SmPC already extended the patent claiming the drug substance. In both cases, a method to use patent claiming a new indication may not be eligible anymore for extension as laid down by the regulation:

> *"Conditions for obtaining a certificate*
>
> *A certificate shall be granted if, in the Member State in which the application referred to in Article 7 is submitted and at the date of that application:*
>
> *[…]*
>
> *(c) the product has not already been the subject of a certificate;*
>
> *(d) the authorisation referred to in point (b) is the first authorisation to place the product on the market as a medicinal product."* [d]

---

[a] 35 USC 156(a)
[b] 35 USC 156(c)(3)
[c] Article 13(2) of Regulation EC/469/2009
[d] Article 3 of Regulation EC/469/2009

In comparison to the U.S. statutes, the European requirements are obviously more restrictive as they tie eligibility for a SmPC to the product rather than the use, for which the product has been approved. Clearly, obtaining a SmPC for a new method to use of a known drug may be very difficult in Europe if that drug was authorized in the EU before or if the patent protecting the drug was already extended.

3.3 Freedom to Operate

Every repurposing strategy would be futile if intellectual and commercial property protection were not diligently analyzed before substantial investments were made. A new indication found for a known drug can only be patented if patent protection of that drug has expired (or never existed) and if no other patent claims the same indication for that drug. Freedom to operate (FTO) means that the risk of patent infringement for drug development programs is greatly reduced. The process leading to this level of confidence is called FTO analysis. The FTO analysis is a systematic dissection of the product or process into its components, which are subsequently examined for patent protection. As only licenses and court rulings establish absolute FTO, every FTO analysis must be carried out as meticulously and diligently as possible to avoid the finding of "wilful infringement" by a court, which can have any damage award multiplied in the event that a third party brings suit for infringement.[33]

While within the scope of this thesis only a brief overview can be given, it should be said that every FTO analysis is time- and cost intensive. Ideally, a skilled cross-functional team with a deep technical and scientific understanding should carry out the analysis. The team's activities will most notably include:

1. Analyzing, understanding and dissecting the technology
2. Recognizing pharmaceutical technical considerations
3. Interviewing the researchers
4. Locating notebooks, lab records, and computer files
5. Finding MTA's (Material Transfer Agreements) and any unknown property trail
6. Formulating the series of FTO questions
7. Selecting scientific databases
8. Selecting patent databases
9. Identifying special resources for pharmaceutical patent information
10. Understanding U.S. (or any other country) Patent and Trademark Office (PTO) information (file wrappers and disclosures)
11. Remaining aware of the 18-month “period of silence” (the period between first effective filing and publication)
12. Maintaining due diligence throughout the FTO analysis [34]

FTO is a key requirement for any repurposing strategy and should be carried out as soon as a candidate drug has been identified.

4 Prospective Health Technology Assessment

4.1 General Considerations

Health Technology Assessments (HTA) attempt to describe the complex relationship between efficacy, effectiveness (i.e. the level of efficacy outside randomized controlled clinical trials), comparative effectiveness, cost benefit ratio as well as social, legal and ethical implications of a therapeutic product.[35] In times of limited public funds and aging societies, HTA has become a particularly important tool for healthcare payers to determine adoption and level of coverage for existing and new medications.[36] Early and ongoing prediction of the outcome of such an assessment is therefore important to every business model, for which commercial success depends on reimbursement. This particularly affects repurposing strategies where a known drug has been found to be a promising candidate in a therapeutic arena where alternative treatments or even cost-effective generics exist. However, in markets where medications are prescribed or administered on a self-payer basis as is the case for cosmetic procedures or treatments, HTA clearly plays much less of a role as medicines agencies such as the FDA, EMA or BfArM typically only issue approval on the basis of risk benefit evaluation.[37] However, certain aspects of HTA such as comparative risk benefit assessment should always be considered by the industry to determine the level of commercial competitiveness.

HTA is a complex subject that countries have implemented in different ways using a broad range of methodologies. Others have extensively reviewed these and common principles were identified.[36-38] In most countries, the determination of additional therapeutic benefit based on the risk benefit is an important part of the comparative evaluation of medicines. Benefit is usually understood as effectiveness. The quality of the trials is a key issue as data on the relevance of trial results for the target patient population are commonly required. Risk is typically understood as the level of toxicity comprised of the type, frequency and severity of adverse drug reactions and drug interactions. Another important aspect of HTA is the evaluation of therapeutic benefit from the patient perspective. Factors such as quality of life, convenience, compliance and satisfaction are typically included in the assessment. Pharmacological and other properties of the pharmaceutical product are also considered. Improved pharmacokinetic properties, new administration routes, improved pharmaceutical forms or packages are included in the assessment albeit tied to the requirement for improved effectiveness or safety. Therefore, such properties are only of secondary importance as they

do not convey additional benefit when viewed alone. Last, the majority of countries compare the cost effectiveness of a pharmaceutical to treatment alternatives that do not necessarily need to be drug-based. While the aforementioned criteria are usually evaluated within a comparative analysis, a number of separate criteria are usually taken into consideration as well. These include the availability of alternative treatments, the level of innovation (e.g. new strength or new combination), social and ethical considerations such as distributive justice and solidarity, and the economic impact on the health budget.[39]

In the U.S., HTA has not yet reached the same level of centralization and coordination as in Western European countries, Canada and Australia. In fact, HTA in the U.S. resembles a fragmented landscape where public and private sector initiatives are scattered across a number of local and national programs. Most notably, the Medicare Coverage Division within the Center for Medicare and Medicaid Services commissions HTA reports. Medicare and Medicaid provide healthcare coverage for more than 60 million individuals. Of diminishing importance is the Agency for Healthcare Research and Quality because of political issues resulting in funding caps and an uncertain future for the agency.[40]

The need for comprehensive clinical data is a major disadvantage of HTA to both the industry and healthcare payers. By the time such data are available (typically post phase IV studies), product development has completed and substantial investments made. A negative HTA at this point could therefore result in significant revenue losses or widespread patient damage because of risks that could not be detected during the clinical phase of development. This was unfortunately the case for Sibutramine, a drug approved for weight loss in the EU and U.S. In 2002, the company was required to conduct the SCOUT (Sibutramine Cardiovascular Outcome Trial) study, which was conceived as a long-term safety study to assess cardiovascular risks such as heart attack and stroke in obese patients. Cardiovascular risks were indeed elevated and, as a result, Sibutramine withdrawn from the market.[41] While the risk of such outcomes is expected to be reduced for repurposed drugs with well-known safety profiles, it cannot be completely ruled out as new risks may arise from the use of known drugs in different target populations. In light of the fact that a number of important drugs such as Sibutramine have been withdrawn from the market in recent years, there is a growing need for methods that identify such risks much earlier in development. [41,42] Methods that may be helpful in predicting risk benefit and cost benefit ratios of drugs early in development have been proposed and are discussed below.

4.2 Preliminary Risk Benefit Assessment

Developing known drugs for new indications offers the advantage to rely on usually substantial human safety databases, which allows for the preliminary conduct of Risk Benefit

Assessments (RBA) before and during development. This is, to the same extent, not possible for first-in-class NME's as reliable data on safety do not yet exist. For some NME's, predictions with regards to safety and efficacy may be possible in the presence of known mode of actions and associated class effects (e.g. pregnancy warning class for antiandrogens).

To date, health authorities do not use common methodology to measure the risk benefit balance of drugs or other treatment forms. The process leading to the decision on the risk benefit balance of any treatment is complex, based on a great body of data and expected to largely remain the subject of expert judgment as stated in the CHMP (Committee Medicinal Products for Human use) reflection paper on risk benefit assessment methods:[43]

> *"The assessment of the benefits and risks in the context of a new drug application is a complex process that requires evaluation of a large amount of data. [...] Expert judgment is expected to remain the cornerstone of benefit-risk evaluation for the authorisation of medicinal products. Quantitative benefit-risk assessment is not expected to replace qualitative evaluation."*

A number of quantitative and semi-quantitative methods ranging from simple decision analysis to complex mathematical models have been proposed. The most important of these are summarized in the aforementioned CHMP reflection paper. The CHMP has identified three principles of risk benefit assessment common to all methods:

> *"* • *The most important benefits and medically serious risks that drive the assessment can be identified more clearly.*
> • *Explicit weights are assigned to individual benefits and risks depending on their importance.*
> • *The strengths of evidence and uncertainty are identified and quantified."*

These principles can be proactively applied to drugs considered for repurposing. Known drugs have usually been exposed to large patient populations for an extended period of time, which largely reduces the uncertainty underlying every risk benefit assessment at the time of approval. In using various methods to determine the severity and frequency of occurrence of risks (reviewed by Guo *et al.*[44]), companies are in the advantageous position to decide prospectively, whether or not the risks of a known drug are expected to outweigh the benefits for the envisaged indication. Without such assessment, development programs may go awry as recently demonstrated by the company Vivus. In December of 2009, Vivus submitted a 505(b)(2) application for the fixed-combination weight loss product Qnexa, which is comprised of the two previously approved drugs Topiramate and Phentermine. Topiramate is a known teratogenic while Phentermine has been associated with serious adverse psychiatric and cardiovasular effects. Vivus pursued a low dose strategy of these compounds to justify chronic use and could indeed show outstanding efficacy of the low-dose combination. Still, the safety concerns overweighed the benefit leading FDA's scientific advisory board to vote against approval, which resulted in a complete response letter from

the FDA rejecting Vivus' NDA and requesting further studies on teratogenic and cardiovascular risks.[45,46] While the jury is still out on the question whether Vivus succeeds in demonstrating a positive risk benefit balance upon resubmission, this example shows how well-known properties of drugs need to be taken into consideration for the targeted indication.

The safety profile of known drugs may not always be carried over to the new indication, as the pharmaceutical form, posology and route of administration can be different. Diclofenac 1% gel (Voltaren) carries a black box warning for cardiovascular and gastrointestinal risks while the 0.1% eye drops do not. Likewise, Tretinoin carries a pregnancy category C warning in the product information for Retin-A and Renova, which are topical creams for the treatment of acne vulgaris and skin irregularities, respectively. Formulations of Tretinoin intended to be administered orally carry a class D warning (e.g. Vesanoid, now discontinued). Clearly, the presence of systemic drug levels rather than concentration alone is the major factor deciding the level of risk category in these two examples. As exposure thresholds, under which adverse events cease to occur, are usually not known for drugs, companies are ill advised to argue along concentration lines as demonstrated by the Qnexa case.

In most cases the drug's known side effects are likely to be of relevance for the new indication. In the absence of any efficacy data it is important to determine whether a drug's risk profile is acceptable for the proposed indication. While thalidomide's risk profile is clearly unacceptable in sleeping aids, the tables are turned for leprosy, multiple myeloma and possibly even dermatological disorders.[47] Drugs withdrawn from the market for safety reasons should therefore not be ruled out for repurposing. Another important point to consider is the addition of risk through changes in the target patient population, which may involve previously unexposed groups for which no safety data exist. As regards Vivus' Qnexa, repurposing a drug with known adverse cardiac and teratogenic effects for weight loss appears to be a risky endeavor as obese patients are already at increased risk for cardiovascular events, let alone the widespread use of such drugs in the female obese population.

As stated previously, the importance of preliminary RBA's is unfortunately accompanied by the lack of simplified methods that allow for a practical and reliable evaluation.[48] In addition, most existing models rely on efficacy data and responder rates, which are not known early in development. The EMA is currently running a 3-year project aimed at identifying appropriate models that allow for consistent and transparent risk benefit evaluations and decisions. Provided that this project will be successfully completed, its outcome ought to provide manufacturers with a more specific and less intuitive decision process for the risk benefit evaluation of known drugs developed for new indications. In the meantime, drug developers

should assess the risk benefit balance of a drug to be repurposed using the principles identified by the CHMP as previously outlined. A simple and practical way of assessing the risk profile of a known drug is proposed in Appendix C.

4.3 Continuous Technology Assessment

While it is important to continuously evaluate the risk benefit profile of a drug in any development program, drug developments also need to be continuously monitored in therapeutic areas where coverage by healthcare payers is crucial for commercial success. Several models have been proposed and reviewed by Bartelmes *et al*.[49] Constructive Technology Assessment (CoTA) is the collective term for a number of methods that subject early developments to a broad scrutiny of HTA-relevant parameters (compare chapter 4.1). Therefore, CoTA can be used to continuously collect data, which are used to influence the development of the product.[50]

An interesting method to achieve a positive HTA outcome is the iterative use of economic evaluation.[51] This method is a staggered approach to shape the development of a product from the early phases to market entry. Indicative studies yielding soft data are initially used and later replaced by hard data from robust comparative analyses, increasing the chance of choosing technologies with the best cost benefit ratio and most solid diffusion into the market. At stage I (early development), current technologies to be replaced by the new product are assessed for their cost benefit ratio and compared to the data available at that point. Key issues are shortcomings in effectiveness of the current technologies to define an effectiveness gap that needs to be filled by the new technology. If the current technology is very effective, the chance of developing a product with an improved cost benefit ratio is small unless costs are greatly reduced. At stage II (maturing innovation), the innovative product has matured enough to estimate its cost benefit ration based on preliminary patient data. While not yet definitive, this analysis is appropriate to define limits for variables, at which a positive risk benefit ratio is likely achieved. At stage III (close to widespread diffusion), data from randomized controlled clinical trials are available. They can be used to update the business model and to determine whether the innovative treatment is cost-effective within the controlled trial population. However, they can usually not be used to determine effectiveness unless data from stage I and II convincingly demonstrate superiority over existing technologies. Stage IV is usually needed to demonstrate effectiveness. At this stage routine clinical use begins (typically after approval). In summary, iterative use of economic evaluation enables drug developers to prepare for the HTA of their innovations and to make development decisions in favor of a positive HTA outcome.[49,51]

As decisions have to be continuously made throughout development, quite a few methods have been established to support decision making such as Analytical Hierarchy Processes, Stated Preference Methods, expert systems, Bayesian methods and decision analytic modelling. While these methods are important to mention, they have been reviewed by others and are not without limitations as “one size fits all” does not exist for any of these methods (compare chapter 4.2).[52,53]

5 Drugs Repurposed for New Indications: Analysis of U.S. and EU Databases

In the U.S., the FDA collects all drug entries in their weekly updated database ‘Drugs@FDA’, which can be downloaded from the FDA website.[54] Note that this database does not contain drugs and biologics not approved under a NDA (e.g. biologics, certain OTC drugs and animal drugs) nor does it include supplements. In the EU, the MRI product index, which is located at the HMA (Heads of Medicines Agencies) website, utilizes a platform that allows to be searched by application type level or other criteria. This database only contains information on products that were authorized through MRP (Mutual Recognition Procedure) or DCP (Decentralized Procedure).[55]

To estimate the proportion of repurposed drugs of all approved drugs, U.S. and EU databases were searched for drugs approved for new indications. The regulatory pathways used for approval were also examined to test if applications were filed under the provisions of Section 505(b)(2) of the FD&C Act and Article 10(3) of Directive 2001/83/EC.

5.1 US: Drugs@FDA Analysis

The database Drugs@FDA was downloaded and formatted as described by the instructions.[54] A total of 17,346 separate application numbers were searched by chemical type as follows:Table 4: Drugs@FDA chemical type codes and description

Chemical Type		
ID	**Code**	**Description**
Blank	Blank	Generic (ANDA)
1	1	New molecular entity (NME) if never marketed in the U.S. before
2	2	New ester, new salt, or other noncovalent derivative
3	3	New formulation
4	4	New combination
5	5	New manufacturer
6	**6**	**New indication**
7	7	Drug already marketed, but without an approved NDA
15	8	OTC (over-the-counter) switch
14	14	New molecular entity (NME) and new combination

23	23	New ester, new salt, or other noncovalent derivative and new formulation
24	24	New ester, new salt, or other noncovalent derivative and new combination
34	34	New formulation and new combination

The database search included both active, discontinued, approved and tentatively approved drugs. While the focus was set on chemical type 6 applications for new indications, chemical type 6 often concerns applications for new indications submitted by the same manufacturer. As Section 505(b)(2) can only be used when non-proprietary studies are referenced, such applications will have to be filed under Section 505(b)(1) if the application contains cross-references to studies from the original dossier (e.g. Bimatoprost for increased growth of eye lashes, NDA 22369). The results show that the vast majority of data entries fall to the category of generic drug applications with 13,313 separate application numbers (Fig. 2 A). Comparable in proportion, applications for new formulations, new molecular entities and new drug manufacturers account for 1365, 1148 and 938 entries. Fixed-combination products contributed 259 entries only.

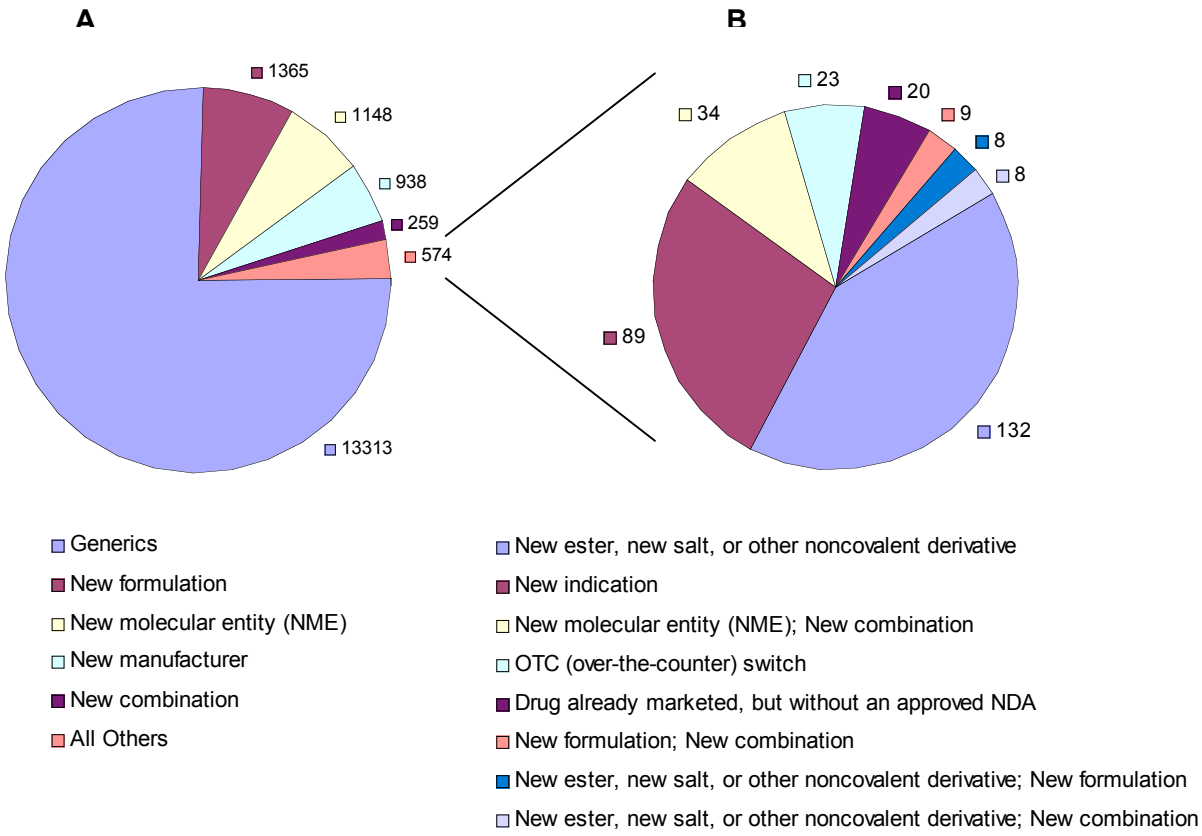

Fig. 2: Drugs@FDA search for drug applications by chemical type

The remaining 574 data entries were combined and split up in a second diagram for more clarity (Fig. 2 B). In this section, applications for new esters, new salts or other noncovalent

derivatives constitute the majority of 132 database entries followed by just 89 applications for new indications. Yet even smaller fractions are contributed by applications for new molecular entities in fixed-combination arrangements (34 entries), OTC drugs (23 entries), drugs marketed without an approved NDA (20 entries), new formulations and fixed-combinations (9 entries), new formulations of new esters, salts or other noncovalent derivatives (8 entries) and new combinations of new esters, salts or other noncovalent derivatives (also 8 entries). With 89 out of a total 4033 nongeneric entries, applications for new indications constitute just 2.2%. Note that Drugs@FDA is not suited for searching different chemical type classes by 505(b)(2) submissions. This information can only be retrieved from the administrative documents and approval letters specific to each application procedure and made publicly available at the online version of Drugs@FDA under the provisions of the Freedom of Information (FOI) Act.[54] However, these documents are usually only accessible for more recent approvals (post year 2000) and even then, consistent demarcation between 505 (b)(1) and 505(b)(2) is often lacking.

In spite of these limitations, the administrative documents of all retrieved applications for new indications were reviewed for 505(b)(2) submissions using the online version of Drugs@FDA. Out of 89 data entries, only 3 could be identified as 505(b)(2) submissions: Triamcinolone acetonide (Triesence, NDA 22223), Omeprazole (Zegerid, NDA 21706) and Tinidazole (Tindamax, NDA 21682). Review of the administrative documents reveals that for Triesence, cross-references were made to a previously approved product containing the same active moiety (RLD: Kenalog-40, NDA 14901) while the submission for Tindamax appeared to be based on literature only. The application for Zegerid contained a combination of both (RLD: Prilosec, NDA 19810). For many applications, the information pertaining to the subsection of 505(b) was not filled out in the application. Still, the majority of applications were, as expected, classified as 505(b)(1) submissions (63 out of 89). 505(b)(2) applications therefore had a share of 3.4% in the group of chemical type 6 submissions.

As many known repositioned drugs were not identified in this analysis, Drugs@FDA was specifically searched for these drugs, which were identified using various internet sources (Table 5).[56-58] Note that this non-exhaustive list was only filled in for repurposed drugs for which NDA's were submitted and listed at Drugs@FDA.

Table 5: Non-exhaustive list of successfully repurposed drugs and legal basis of submission

Examples of repurposed drugs identified in Drugs@FDA					
Drug Name	**NDA**	**Chemical Type**	**Initial Indication**	**New Indication**	**Legal Basis**
Allopurinol	20298	3 (New formulation)	Cancer	Gouty arthritis	N/A
Arsenic	21248	1 (NME)	Syphilis	Leukemia (Orphan)	505(b)(1)

Aspirin	20884	4 (New combination with Dipyridamole)	Analgesic	Antiplatelet	505(b)(2)
Atomoxetine	21411	1 (NME)	Depression	ADHD	505(b)(1)
Bupropion	20711	3 (New formulation)	Depression	Smoking cessation	N/A
Doxepin	22036	3 (New formulation)	Depression	Insomnia	505(b)(2)
Finasteride	20788	3 (New formulation)	Prostate cancer	Hair loss	505(b)(1)
Gabapentin	22399	1 (NME)	Epilepsy	Restless Leg Syndrome	505(b)(2)
Naltrexone	21897	3 (New formulation)	Opioid addiction therapy	Alcohol withdrawal therapy	505(b)(2)
Nitric oxide	20845	1 (NME)	Angina	Pulmonary hypertension	N/A
Ralofixene	20815	1 (NME)	Contraceptive	Menopausal osteoporosis	N/A
Thalidomide	20785	1 (NME)	Antiemetic / insomnia	Erythema nodosum leprosum	505(b)(2)
Thalidomide	21430	6 (New Indication)	Antiemetic / insomnia	Multiple myeloma (Orphan)	N/A
Tretinoin	20438	3 (New formulation)	Severe acne	Leukemia	N/A

Table 5 shows that applications for new indications were frequently filed under the provisions of 505(b)(2) using different chemical type classifications. These included new combinations, new formulations and, remarkably, NME's that had not been approved for their original indication the U.S. before. For a few, information on the subsection of Section 505(b) used was again not available (N/A).

5.2 EU: MRI Product Index Analysis

In the EU, drugs can be approved for new indications using Hybrid-Applications under the provisions of Article 10(3) of Directive 2001/83/EC or MMAA's under the provisions of Annex I Part II No. 7 of Directive 2001/83/EC (compare chapter 2.3.1). PUMA's represent a very new and specific form of repurposing for children, and are therefore not further considered here. The MRI Product Index was searched to access the extent to which these two regulatory routes were used for repurposing in the EU. This index lists more than 20,200 data entries for pharmaceuticals and line extensions that can be searched by multiple criteria including RMS (Reference Member State), CMS (Concerned Member State), end of procedure date (day 90) and application type level (L1 – L5).[55] Application type level 3 lists Article 10(3) applications amongst other search criteria, which can be combined with a number of different criteria listed for the other levels. Table 5 summarizes the combinations used for the first search. Note that all searches were restricted to chemical substances subject to prescription.

Table 6: Search criteria used to identify Article 10(3) applications in the MRI Product Index

Combinations of search criteria				
Level	**Search 1**	**Search 2**	**Search 3**	**Search 4**
L1	Known active substance	Known active substance	Known active substance	Abridged
L2	Initial application	Initial application	Initial application	Initial Application
L3	Full dossier Art 8(3) Directive 2001/83/EC	Art 10a Directive 2001/83/EC	Art 10(3) Directive 2001/83/EC	Art 10(3) Directive 2001/83/EC
L4	Chemical Substance	Chemical Substance	Chemical Substance	Chemical Substance
L5	Prescription only	Prescription only	Prescription only	Prescription only
Hits	121 (51*)	89	0	332 (126*)

*Number of applications, for which public assessment reports are available

Results show that initial applications for known active substances did not precipitate hits for drug products approved under Article 10(3) of Directive 2001/83/EC (Search 3). 121 data entries could be retrieved for full Article 8(3) applications (Search 1) and 89 for well-established use applications (Article 10a), which do not require conduct of preclinical and clinical studies. While certainly outstanding in terms of R&D productivity, they do not convey much innovation as they only transfer established therapeutic use to approved therapeutic use. When level type 1 was changed from ‘known active substance’ to ‘abridged’ (Search 4), Article 10(3) applications produced 332 hits.

To estimate the proportion of products developed for new clinical use within this group (Search 4) of pharmaceuticals, excluding data entries for which no Public Assessment Report (PAR) exists further narrowed the search. This yielded a total of 126 entries, for which the reports could be reviewed for the presence of clinical studies supporting new clinical use. Out of all entries, applications for new indications could not be identified. All 126 applications were generic / hybrid in nature and only contained slight modifications from the reference drugs, such as different strengths or new formulations, for which therapeutic equivalence studies were conducted in some cases.

Similarly to applying search 4 criteria (Table 5) to data entries for which PAR's were available, search 1 criteria were also applied. 51 data entries could be identified when the search was limited to the presence of PAR's (Table 5). Out of these 51 full dossier applications, 13 approved for new or modified indications were identified. The remaining 38 applications were line extensions (3), new formulations (4), new combinations (3), NME's (3) and others such as 'me-too' and informed consent applications (25). These results are summarized in Fig. 6.

The MRI product Index was also searched for the repurposed drugs listed in table 5. Data entries were found for Atomoxetine, Bupropion, Finasteride, Nitric oxide and Triamcinolone. They all got approved in the EU through full dossiers. Arsenic and Thalidomide, which are

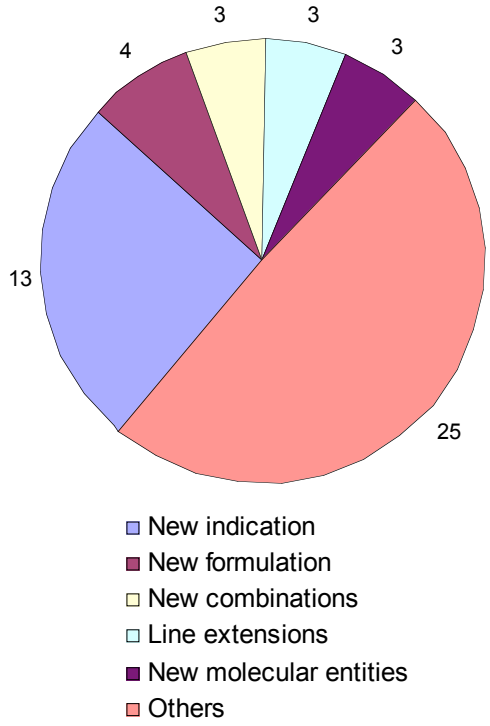

Fig. 6: MRI Product Index search for Art. 8(3) applications for known active substances

also orphan drugs for the indications leukemia and multiple myeloma in the EU, were approved though the centralized procedure as mandated by Regulation EC/729/2004. These results are summarized in table 7. Similar to the U.S., applications for drug substances such as Atomoxetine and Bupropion were also classified as new active substances that were not approved in the EU before. Note that for Nitric oxide and the indication pulmonary hypertension, Article 10a of Directive 2001/83/EC was used as the legal basis of the application as only bibliographical data were submitted.

Table 7: Non-exhaustive list of successfully repurposed drugs and legal basis of submission

Examples of repurposed drugs listed in the MRI Produc Index and EMA database					
Drug Name MR Number	**Level 1**	**Level 2**	**Level 3**	**Level 4**	**Level 5**
Arsenic EMEA/H/C/000388	Orphan drug for leukemia approved via centralized procedure				
Atomoxetine UK/H/0686/001/ /	New active substance	Initial application	Full dossier (Art. 8(3))	Chemical substance	Prescription only
Bupropion NL/H/0192/001/ /	New active substance	Initial application	Full dossier (Art. 8(3))	Chemical substance	Prescription only
Finasteride SE/H/0158/001/E001/	Active substance	Repeat use	Full dossier (Art. 8(3))	Chemical substance	Prescription only
Nitric oxide BE/H/0134/001/DC	Known active substance	Initial application	Established use (Art. 10a)	Chemical substance	Prescription only

Thalidomide EMEA/H/C/000823	Orphan drug for multiple myeloma approved via centralized procedure				
Triamcinolone DE/H/2294/001/DC	Known active substance	Initial application	Full dossier (Art. 8(3))	Chemical substance	Prescription only

While this analysis does not claim to be conclusive and use of Article 10(3) for new indications cannot be entirely ruled out, it is obvious that the provisions of this Article for new indications have not been used by the industry for the repurposing of drugs. Instead, the industry submits full dossiers on the basis of Article 8(3) for new indications.

6 Discussion

In this comparative analysis, substantial differences between U.S. and EU regulations were identified and confirmed by targeted drug database searches. In the U.S., applications filed under the provisions of Section 505(b)(2) of the FD&C Act can be tailored to the specific change form the RLD and may contain reduced dossiers as cross-references to other studies or approved products are explicitly permitted. Data exclusivity terms depend on the novelty of the drug substance rather than the legal basis on which the application is filed. These terms are also comparable with 5 and 3 years for NME's and previously approved drug substances. Data exclusivity extensions for pediatric studies are not tied to patent term extensions and can thus be granted to 505(b)(1) as well as 505(b)(2) applications. A major difference appears to be the conditions under which patent term extensions are granted, though. In the U.S., patent term extensions are tied to the approval of an application and the term of the patent regardless of whether or not the drug substance was authorized in the U.S. before. Therefore, method to use patents, which are key to the commercial success of repurposed drugs, can be extended even if the drug substance was approved for a different indication before. Contrary to the EU, U.S. regulations analogous to PUMA do not exist. Drug development programs exclusively for the pediatric population are therefore not rewarded with extended data and market protection. While this makes the EU a more attractive market for such developments, they have not been extensively used so far. As a matter of fact, since the Pediatric Regulation came into force in 2007, only one PUMA has been authorized thus far.[59] It remains to be seen if the PUMA regulation will turn out to be successful.

In the EU, regulations are divided into such that allow use of bibliographical data and others that permit cross-reference to approved products. Annex I Part II No. 7 and No. 1 permit use of bibliographical data in MMAA's, which contain full dossiers that must be filed under the provisions of Article 6 and 8(3) of Directive 2001/83/EC to obtain the same data and market protection as applications containing the full set of preclinical and clinical studies (unless the new indication has been registered for a well-established drug, in which case only one year

of data exclusivity is granted). However, these regulations do not allow for applications on the basis of reduced data packages and cross-references to previously approved products. Contrary to the U.S., such applications are only permitted within the framework of Article 10 for generics, hybrids and biosimilars. Article 10(3) provides provisions similar to Section 505(b)(2) and even includes changes of the indication. In contrast to 505(b)(2) it is not used for such developments. This is in the absence of any market protection for generics an understandable outcome. In addition to these shortcomings, method-to-use patents are weaker in the EU when compared to the U.S. as patent term extensions for previously authorized or extended drug substances are likely not issued in the EU. Therefore, patent extension in return of PIP compliance cannot be granted, which appears to be a serious flaw of these regulations. Short of Article 10, only the PUMA regulation allows cross-references to authorized products. As previously stated, PUMA only appears to be welcome by niche developments and may not play a significant future role in drug repurposing. This is hardly offset by the fact that in the EU, incentives for orphan drugs and PUMA's exceed their U.S. counterparts. In conclusion, the regulatory environment of the EU provides much less support for drug repurposing than the U.S.

Current examples of failed approvals show that drug companies sometimes struggle with the right strategy to develop known drugs in new therapeutic areas. Misjudging the risk benefit ratio of an envisaged treatment or failure to determine FTO can result in substantial investment losses. FTO is a crucial requirement of every repurposing strategy and needs to be established before substantial investments are made. Finding FTO or filing patent claims may be a hurdle in a very competitive and nationally organized IP environment, though.

A practical method to judge the risk benefit balance of future treatments has been proposed (Appendix C). Albeit not without limitations, this method seems suitable to identify unacceptable risks and risk levels. Furthermore, it can be adjusted to fulfill individual requirements as the information existing in the beginning can change along the way. The method presented seems best suited when alternative candidates or treatments exist, against which new treatments always ought to be benchmarked. The continuous RBB assessment of a new technology is only part of a further reaching technology assessment. As the cost benefit assessment of new treatments has made its way as a fourth hurdle in most important markets, companies planning on coverage by healthcare payers would be ill-advised not to implement measures of assessing the risk benefit ratio and cost effectiveness throughout development. This is a challenging task as the HTA landscape is still in great disarray, intransparent and far from harmonized. Numerous methods of assessing HTA parameters exist. In consideration of their number, complexity and limitations only a brief introduction could be given in this work.

In light of these findings, a regulatory strategy for drug repurposing in the U.S. and EU is proposed. Every repurposing strategy should begin with the scientific evaluation of the envisaged indication in terms of drug targets, target population, level of UMN and TPP. Drug libraries and databases such as the NPC should facilitate the identification of potential drugs. Identified candidates should subsequently be assessed by their risk benefit balance for the target indication following the CHMP principles of RBA. One major advantage over traditional development of NME's is the possibility to prospectively address these issues before development starts. The method presented in this work may help decide whether or not the RBB of drugs under consideration is acceptable. Promising candidates must be subjected to an FTO analysis before substantial investments are made. These activities ought to be accompanied by regulatory assessments determining study requirements, approval routes as well as regulatory requirements and incentives. Measures for continuous technology assessment should be implemented, particularly when reimbursement is an essential part of the business model. Overviews of these strategic and regulatory considerations are summarized in the decision tree shown in fig. 7, and table 8 (Appendix D).

In summary, the repurposing of known drugs is not a stranger to industry. However, as drugs successfully revived for new indications are still relatively low in numbers, it appears that the full potential of this strategy, which is truly innovative, lower risk and cost-effective, has not been realized yet. European policy makers have clearly not yet realized the innovative potential of repurposed drugs in terms of efficacy, patient safety and time to market, as current regulations do not reflect these obvious advantages. As the repurposing of known drugs could also be an attractive business model for the generics industry, Article 10 of Directive 2001/83/EC should be revised to support the submission of reduced applications for new indications and include adequate protection terms. Likewise, requirements for obtaining the SmPC should be changed to reliably reward these innovative developments with extended patent protection and pediatric SmPC extensions.

Summary

In the face of higher development risks due to tight regulatory and cost benefit scrutiny, drug companies are under growing pressure to increase R&D productivity and to decrease investment costs. One effective way of tackling these challenges is to develop qualified drugs in new therapeutic areas while relying on investigations already conducted for these drugs. This approach, commonly known as repurposing, has the potential to be truly innovative, cost-effective and lower risk. 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 health and healthcare payers, European legislators should increase their efforts to facilitate such developments.

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Appendix A

FDA Guidance for Industry: Applications Covered by Section 505(b)(2)

Guidance for Industry

Applications Covered by Section 505(b)(2)

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on the content of the draft document contact Virginia Beakes, (301) 594-2041.

U. S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 1999

Guidance for Industry

Applications Covered by Section 505(b)(2)

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 1999

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Draft - Not for Implementation

GUIDANCE FOR INDUSTRY[1]

Applications Covered by Section 505(b)(2)

I. WHAT IS THE PURPOSE OF THIS GUIDANCE?

This guidance identifies the types of applications that are covered by section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act). A 505(b)(2) application is a new drug application (NDA) described in section 505(b)(2) of the Act. It is submitted under section 505(b)(1) of the Act and approved under section 505(c) of the Act. This guidance also provides further information and amplification regarding FDA's regulations at 21 CFR 314.54.

Section 505 of the Act describes three types of new drug applications: (1) an application that contains full reports of investigations of safety and effectiveness (section 505(b)(1)); (2) an application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (section 505(b)(2)); and (3) an application that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product (section 505(j)). Note that a supplement to an application is a new drug application.

Section 505(b)(2) was added to the Act by the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments). This provision expressly permits FDA to rely, for approval of an NDA, on data not developed by the applicant. Sections 505(b)(2) and (j) together replaced FDA's *paper NDA policy*, which had permitted an applicant to rely on studies published in the scientific literature to demonstrate the safety and effectiveness of duplicates of certain post-1962 pioneer drug products (see 46 FR 27396, May 19, 1981). Enactment of the generic drug approval provision of the Hatch-Waxman Amendments ended the need for approvals of duplicate drugs through the paper NDA process by permitting approval under 505(j) of duplicates of approved drugs (listed

[1]This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the types of applications that may be submitted pursuant to section 505(b)(2) of the Act. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

drugs) on the basis of chemistry and bioequivalence data, without the need for evidence from literature of effectiveness and safety. Section 505(b)(2) permits approval of applications other than those for duplicate products and permits reliance for such approvals on literature or on an Agency finding of safety and/or effectiveness for an approved drug product.

Definitions for specific terms used throughout this guidance are given in the Glossary.

II. WHAT IS A 505(B)(2) APPLICATION?

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" (21 U.S.C. 355(b)(2)).

A. What type of information *can* an applicant rely on?

What type of information can an applicant rely on in an application that is based upon studies "not conducted by or for the applicant and for which the applicant has not obtained a right of reference?"

1. Published literature

An applicant should submit a 505(b)(2) application if approval of an application will rely to any extent on published literature (a *literature-based* 505(b)(2)). If the applicant has not obtained a right of reference to the raw data underlying the published study or studies, the application is a 505(b)(2) application; if the applicant obtains a right of reference to the raw data, the application may be a full NDA (i.e., one submitted under section 505(b)(1)). An NDA will be a 505(b)(2) application if any of the specific information necessary for approval is obtained from literature or from another source to which the applicant does not have a right of reference, even if the applicant also conducted clinical studies to support approval. Note, however, that this does not mean ***any*** reference to published general information (e.g., about disease etiology, support for particular endpoints, methods of analysis) or to general knowledge causes the application to be a 505(b)(2) application. Rather, reference should be to specific information (clinical trials, animal studies) necessary to the approval of the application.

2. The Agency's finding of safety and effectiveness for an approved drug

An applicant should submit a 505(b)(2) application for a change in a drug when approval of the application relies on the Agency's previous finding of safety and/or effectiveness for a drug. This mechanism, which is embodied in a regulation at 21 CFR 314.54, essentially makes the Agency's conclusions that would support the approval of

a 505(j) application available to an applicant who develops a modification of a drug. Section 314.54 permits a 505(b)(2) applicant to rely on the Agency's finding of safety and effectiveness for an approved drug to the extent such reliance would be permitted under the generic drug approval provisions at section 505(j). This approach is intended to encourage innovation in drug development without requiring duplicative studies to demonstrate what is already known about a drug while protecting the patent and exclusivity rights for the approved drug.

It is possible that an applicant could submit a 505(b)(2) application that relies both on literature and upon the Agency's finding of safety and effectiveness for a previously approved drug product (e.g., to support a new claim).

B. What kind of application can be submitted as a 505(b)(2) application?

1. New chemical entity (NCE)/new molecular entity (NME)

A 505(b)(2) application may be submitted for an NCE when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and to which the applicant has not obtained a right of reference. For an NCE, this data is likely to be derived from published studies, rather than FDA's previous finding of safety and effectiveness of a drug. If the applicant had a right of reference to all of the information necessary for approval, even if the applicant had not conducted the studies, the application would be a considered a 505(b)(1) application.

2. Changes to previously approved drugs

For changes to a previously approved drug product, an application may rely on the Agency's finding of safety and effectiveness of the previously approved product, coupled with the information needed to support the change from the approved product. The additional information could be new studies conducted by the applicant or published data. This use of section 505(b)(2), described in the regulations at 21 CFR 314.54, was intended to encourage innovation without creating duplicate work and reflects the same principle as the 505(j) application: it is wasteful and unnecessary to carry out studies to demonstrate what is already known about a drug. The approach was described in a letter to industry dated April 10, 1987, from Dr. Paul D. Parkman, then Acting Director of the Center for Drugs and Biologics. This guidance helps to clarify and amplify the approaches stated in the April 10, 1987, letter and in the regulations.

An applicant should file a 505(b)(2) application if it is seeking approval of a change to an approved drug that would not be permitted under section 505(j), because approval will require the review of clinical data. However, section 505(b)(2) applications should

not be submitted for duplicates of approved products that are eligible for approval under 505(j) (see 21 CFR 314.101(d)(9)).

In addition, an applicant may submit a 505(b)(2) application for a change in a drug product that is eligible for consideration pursuant to a suitability petition under Section 505(j)(2)(C) of the Act. In the preamble to the implementing regulations for the Hatch-Waxman amendments to the Act, the Agency noted that an application submitted pursuant to section 505(b)(2) of the Act is appropriate even when it could also be submitted in accordance with a suitability petition as defined at section 505(j)(2)(C) of the Act (see 57 FR 17950; April 28, 1992).

III. WHAT ARE SOME EXAMPLES OF 505(B)(2) APPLICATIONS?

Following are examples of changes to approved drugs for which 505(b)(2) applications should be submitted. Please note that in particular cases, changes of the type described immediately below may not require review of information other than BA or BE studies or data from limited confirmatory testing.[2] In those particular cases, approval of the drug may also be sought in a 505(j) application based on an approved suitability petition as described in section 505(j)(2)(C) of the Act. The descriptions below address the situation in which the application should be filed as a 505(b)(2) application because approval of the application will require review of studies beyond those that can be considered under section 505(j). Some or all of the additional information could be provided by literature or reference to past FDA findings of safety and effectiveness for approved drugs, or it could be based upon studies conducted by or for the applicant or to which it has obtained a right of reference.

- *Dosage form.* An application for a change of dosage form, such as a change from a solid oral dosage form to a transdermal patch, that relies to some extent upon the Agency's finding of safety and/or effectiveness for an approved drug.

- *Strength.* An application for a change to a lower or higher strength.

- *Route of administration*. An application for a change in the route of administration, such as a change from an intravenous to intrathecal route.

- *Substitution of an active ingredient in a combination product*. An application for a change in one of the active ingredients of an approved combination product for another active ingredient that has or has not been previously approved.

Following are additional examples of applications that may be accepted pursuant to section 505(b)(2) of the Act. Some or all of the additional information could be provided by the literature or reference to

[2] Limited confirmatory testing is explained in further detail in 54 FR 288872, 28880 (July 10, 1989) and 57 FR 17950, 17957-58 (April 28, 1992).

past FDA findings of safety and effectiveness for approved drugs, or it could be based on studies conducted by or for the applicant or to which it has obtained a right of reference.

- *Formulation.* An application for a proposed drug product that contains a different quality or quantity of an excipient(s) than the listed drug where the studies required for approval are beyond those considered limited confirmatory studies appropriate to a 505(j) application.

- *Dosing regimen*. An application for a new dosing regimen, such as a change from twice daily to once daily.

- *Active ingredient*. An application for a change in an active ingredient such as a different salt, ester, complex, chelate, clathrate, racemate, or enantiomer of an active ingredient in a listed drug containing the same active moiety.

- *New molecular entity.* In some cases a new molecular entity may have been studied by parties other than the applicant and published information may be pertinent to the new application. This is particularly likely if the NME is the prodrug of an approved drug or the active metabolite of an approved drug. In some cases, data on a drug with similar pharmacologic effects could be considered critical to approval.

- *Combination product*. An application for a new combination product in which the active ingredients have been previously approved individually.

- *Indication*. An application for a not previously approved indication for a listed drug.

- *Rx/OTC switch*. An application to change a prescription (Rx) indication to an over-the-counter (OTC) indication.

- *OTC monograph.* An application for a drug product that differs from a product described in an OTC monograph (21 CFR 330.11), such as a nonmonograph indication or a new dosage form.

- *Naturally derived or recombinant active ingredient.* An application for a drug product containing an active ingredient(s) derived from animal or botanical sources or recombinant technology where clinical investigations are necessary to show that the active ingredient is the same as an active ingredient in a listed drug.

- *Bioinequivalence*. Generally, an application for a pharmaceutically equivalent drug product must be submitted under section 505(j) of the Act and the proposed product must be shown to be bioequivalent to the reference listed drug (21 CFR 314.101(d)(9)). Applications for proposed drug products where the rate (21 CFR 314.54(b)(2)) and/or extent (21 CFR 314.54(b)(1)) of absorption exceed, or are otherwise different from, the 505(j) standards for bioequivalence compared to a listed drug may be submitted pursuant to section 505(b)(2) of the

Act. Such a proposed product may require additional clinical studies to document safety and efficacy at the different rate and extent of delivery. Generally, the differences in rate and extent of absorption should be reflected in the labeling of the 505(b)(2) product. The proposed product does not need to be shown to be clinically *better* than the previously approved product; however, a 505(b)(2) application should not be used as a route of approval for poorly bioavailable generic drug products unable to meet the 505(j) standards for bioequivalence. If the proposed product is a duplicate of an already approved product, it should not be submitted as a 505(b)(2) application (21 CFR 314.101(d)(9)).

For example, a 505(b)(2) application would be appropriate for a controlled release product that is bioinequivalent to a reference listed drug where:

1. The proposed product is at least as bioavailable as the approved pharmaceutically equivalent product (unless it has some other advantage, such as smaller peak/trough ratio); or

2. The pattern of release of the proposed product, although different, is at least as favorable as the approved pharmaceutically equivalent product.

IV. WHAT CAN'T BE SUBMITTED AS 505(B)(2) APPLICATIONS?

- An application that is a duplicate of a listed drug and eligible for approval under section 505(j) (see 21 CFR 314.101(d)(9)); or,

- An application in which the *only* difference from the reference listed drug is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than the listed drug (21 CFR 314.54(b)(1)); or,

- An application in which the *only* difference from the reference listed drug is that the rate at which its active ingredient(s) is absorbed or otherwise made available to the site of action is *unintentionally* less than that of the listed drug (21 CFR 314.54(b)(2)).

V. WHY DOES IT MATTER IF AN NDA IS A 505(B)(2) APPLICATION?

Unlike a full NDA for which the sponsor has conducted or obtained a right of reference to all the data essential to approval, the filing or approval of a 505(b)(2) application may be delayed due to patent or exclusivity protections covering an approved product. Section 505(b)(2) applications must include patent certifications described at 21 CFR 314.50(i) and must provide notice of certain patent certifications to the NDA holder and patent owner under 21 CFR 314.52.

VI. PATENT AND EXCLUSIVITY PROTECTIONS THAT COULD AFFECT A 505(B)(2) APPLICATION

A. What type of patent and/or exclusivity protection is a 505(b)(2) application eligible for?

A 505(b)(2) application may itself be granted 3 years of Waxman-Hatch exclusivity if one or more of the clinical investigations, other than BA/BE studies, was essential to approval of the application and was conducted or sponsored by the applicant (21 CFR 314.50(j); 314.108(b)(4) and (5)). A 505(b)(2) application may also be granted 5 years of exclusivity if it is for a new chemical entity (21 CFR 314.50(j); 314.108(b)(2)). A 505(b)(2) application may also be eligible for orphan drug exclusivity (21 CFR 314.20-316.36) or pediatric exclusivity (section 505A of the Act).

A 505(b)(2) application must contain information on patents claiming the drug or its method of use (21 CFR 314.54(a)(1)(v)).

B. What could delay the approval or filing of a 505(b)(2) application?

Approval or filing of a 505(b)(2) application, like a 505(j) application, may be delayed because of patent and exclusivity rights that apply to the listed drug (21 CFR 314.50(i), 314.107, and 314.108 and section 505A of the Act). This is the case even if the application also includes clinical investigations supporting approval of the application.

VII. WHAT SHOULD BE INCLUDED IN 505(B)(2) APPLICATIONS?

The Act (sections 505(b)(1) and (b)(2)) and FDA regulations (21 CFR 314.54) distinguish between 505(b)(1) and (b)(2) applications. Although the two types of applications must meet the same standards for approval (see section 505(b) and (c) of the Act), they differ in source of information to support safety and effectiveness, the patent certification requirements, BA/BE evidence, exclusivity bars, and processing within the FDA. The requirements for 505(b)(1) and 505(b)(2) applications are described at 21 CFR 314.50. Additional requirements for certain 505(b)(2) applications are described at 21 CFR 314.54.

A 505(b)(2) application should include the following:

- Identification of those portions of the application that rely on information the applicant does not own or to which the applicant does not have a right of reference (for example, for reproductive toxicity studies).

- If the 505(b)(2) seeks to rely on the Agency's previous finding of safety or efficacy for a listed drug or drugs, identification of any and all listed drugs by established name, proprietary name (if

any), dosage form, strength, route of administration, name of the listed drug's sponsor, and the application number (21 CFR 314.54(a)(1)(iii)). Even if the 505(b)(2) application is based solely upon literature and does not rely expressly on an Agency finding of safety and effectiveness for a listed drug, the applicant must identify the listed drug(s) on which the studies were conducted, if there are any. If the 505(b)(2) application is for an NCE and the 505(b)(2) applicant is not relying on literature derived from studies of an approved drug, there may not be a listed drug. If there is a listed drug that is the pharmaceutical equivalent to the drug proposed in the 505(b)(2) application, that drug should be identified as the listed drug.

- Information with respect to any patents that claim the drug or the use of the drug for which approval is sought (21 CFR 314.50(h)). This patent information will be published in the Orange Book when the application is approved.

- Information required under 314.50(j) if the applicant believes it is entitled to marketing exclusivity (21 CFR 314.54(a)(1)(vii)).

- A patent certification or statement as required under section 505(b)(2) of the Act with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug (21 CFR 314.54(a)(1)(vi)).

  If there is a listed drug that is the pharmaceutical equivalent of the drug proposed in the 505(b)(2) application, the 505(b)(2) applicant should provide patent certifications for the patents listed for the pharmaceutically equivalent drug. Patent certifications should specify the exact patent number(s), and the exact name of the listed drug or other drug even if all relevant patents have expired.

- If an application is for approval of a new indication, and not for the indications approved for the listed drug, a certification so stating (21 CFR 314.54(a)(1)(iv).

- A statement as to whether the listed drug(s) identified above have received a period of marketing exclusivity (21 CFR 314.108(b)). If a listed drug is protected by exclusivity, filing or approval of the 505(b)(2) application may be delayed.

- A Bioavailability/Bioequivalence (BA/BE) study comparing the proposed product to the listed drug (if any).

- Studies necessary to support the change or modification from the listed drug or drugs (if any). Complete studies of safety and effectiveness may not be necessary if appropriate bridging studies are found to provide an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s).

Before submitting the application, the applicant should submit a plan to the appropriate new drug evaluation division identifying the types of bridging studies that should be conducted. The applicant should also identify those components of its application for which it expects to rely on FDA's finding of safety and effectiveness of a previously approved drug product. The division will critique the plan and provide guidance.

REFERENCES

April 10, 1987, letter from then Acting Director of the Center for Drugs and Biologics to all NDA and ANDA holders and applicants.

"Abbreviated New Drug Application Regulations; Proposed Rule," *Federal Register*. Vol. 54, No. 130, Monday, July 10, 1989, page 28872.

"Abbreviated New Drug Regulations; Final Rule," *Federal Register*. Vol. 57, No. 82, Tuesday, April 28, 1992, page 17950.

"Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions; Final Rule," *Federal Register*. Vol. 59, No. 190, Monday, October 3, 1994, page 50338.

GLOSSARY

505(b)(2) application: an application submitted under section 505(b)(1) of the Act for a drug for which one or more of the investigations relied on by the applicant for approval of the "application 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" (21 U.S.C. 355(b)(2)).

Active ingredient: "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or of animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect" (21 CFR 60.3(b)(2)).

Active moiety*:* "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance" (21 CFR 314.108(a)).

Investigations relied on for approval: those without which the application cannot be approved (i.e., animal and human safety tests as well as clinical investigations of effectiveness).

Listed drug: "a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the list) or any current supplement thereto, as a drug with an effective approval. A drug product is deemed to be a listed drug on the date of effective approval of the application or abbreviated application for that drug product" (21 CFR 314.3(b)).

Literature: published reports of well-controlled studies that support safety or effectiveness; proposed and final monographs published in the *Federal Register*; the data supporting a *Federal Register* notice announcing a product's safety and/or effectiveness.

Orange Book: *Approved Drug Products with Therapeutic Equivalence Evaluations* and any current supplement to the publication.

Pharmaceutical equivalent or duplicate*:* "drug products that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, in identical dosage forms, but not necessarily containing the same inactive ingredients, and that meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and,

where applicable, content uniformity disintegration times and/or dissolution rates" (21 CFR 320.1(c)). Products with different mechanisms of release can be considered to be pharmaceutical equivalents or duplicates.

Referenced listed drug: "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3(b)).

Right of reference or use: "the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an application, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary" (21 CFR 314.3(b)).

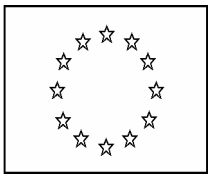
Sponsors have the right of reference to any studies: (1) they conduct, (2) that are conducted for them, or (3) for which they formally obtain a documented *right of reference*.

An applicant is not considered to have a *right of reference* to published studies, because the applicant does not have access to the raw data. However, if the raw data are in the public domain, a right of reference is unnecessary.

Suitability petition: A citizen petition submitted to the Agency seeking permission to file an abbreviated new drug application for a change from a listed drug in dosage form, strength, route of administration, or active ingredient in a combination product. (See section 505(j)(2)(C) of the Act)

Appendix B

Guidance on a new therapeutic indication for a well-established substance



EUROPEAN COMMISSION

ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Brussels, November 2007

GUIDANCE ON A NEW THERAPEUTIC INDICATION FOR A WELL-ESTABLISHED SUBSTANCE

November 2007

GUIDANCE ON A NEW THERAPEUTIC INDICATION FOR A WELL-ESTABLISHED SUBSTANCE

Table of contents

1. Introduction

Paragraph 5 of Article 10 of Directive 2001/83/EC, as amended by Directive 2004/27/EC, states that where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication.

The aim of this guidance is to describe "significant preclinical or clinical studies" and to outline the principles and procedure for the assessment.

2. Principles and procedure

Applicants for a new therapeutic indication should provide the authority assessing the application with any relevant information for the assessment of whether the application concerns "a new therapeutic indication" and whether "significant preclinical or clinical studies" have been carried out in relation to this new indication.

This information should be presented in the form of a report and this should be included in Module 1 of the application for marketing authorisation; related study reports and supporting literature references should be placed in relevant modules of the dossier and cross-referred to accordingly. If the product has been granted access to the Centralised Procedure, the EMEA scientific committees will assess whether significant preclinical or clinical studies have been carried out in relation to this new indication. Likewise the reference member state will make this assessment for applications to the mutual recognition and decentralised systems and the relevant national competent authority will conduct the assessment for purely national applications. This assessment will be performed as part of the procedure within the normal timelines laid down in legislation. Where necessary, questions on the significance of studies may be part of the request for supplementary information to be addressed by the applicant.

For applications for centralised marketing authorisations the Committee on Human Medicinal Products shall adopt a single opinion, which will cover whether significant preclinical or clinical studies have been carried out in relation to the new indication, with the opinion on the scientific assessment of the new indication for the purpose of authorisation. The applicant may ask for re-examination of the opinion following the usual conditions and procedures for re-examination of an opinion (Article 9(2) of Regulation (EC) No 726/2004).

The findings of "significant pre-clinical or clinical studies" will be described in the European Public Assessment Report.

3. General guidance on the preparation of the report justifying that significant preclinical or clinical studies have been carried out in relation to the new indication

The justification that significant preclinical or clinical studies have been carried out in relation to the new indication should be in the form of a short report (in general not more than 5-10 pages), which should include:

- Introduction

- Justification of the new indication compared to the existing therapeutic indication(s):

For the purpose of the implementation of Article 10(5), a “new therapeutic indication” may refer to either diagnosis, prevention or treatment of a disease.

The MAH should provide a justification for the proposed new indication, supported by appropriate scientific information.

No definition of new indication exists in Community legislation, however, Notice to Applicants "A Guideline on Summary of Product Characteristics" states in its section 4.1 "The indication(s) should be stated clearly and concisely and should define the target disease or condition distinguishing between treatment (symptomatic, curative or modifying the evolution or progression of the disease), prevention (primary or secondary) and diagnostic indication. When appropriate it should define the target population especially when restrictions to the patient populations apply".

In this context a new indication would normally include the following:

- a new target disease,
- different stages or severity of a disease
- an extended target population for the same disease, e.g. based on a different age range or other intrinsic (e.g. renal impairment) or extrinsic (e.g. concomitant product) factors
- change from the first line treatment to second line treatment (or second line to first line treatment), or from combination therapy to monotherapy, or from one combination therapy (e.g. in the area of cancer) to another combination,
- change from treatment to prevention or diagnosis of a disease.
- change from treatment to prevention of progression of a disease or to prevention of relapses of a disease
- change from short-term treatment to long-term maintenance therapy in chronic disease.

- Justification that significant preclinical or clinical studies have been carried out in relation to the new indication:

The significance of the preclinical or clinical studies will be evaluated by the EMEA scientific committees or National Competent Authority on a case-by-case basis, however, guiding principles are:

- The applicant should summarize in this report the new preclinical and/or clinical studies carried out in relation to the new indication, and why these should be viewed as significant preclinical or clinical studies.

- The applicant should include his own preclinical and/or clinical studies into the dossier. “Own” means that such investigations have been conducted or sponsored by the applicant.

- In principle, when applying for marketing authorisation for a new indication, it is expected that the applicant has carried out at least one confirmatory clinical trial versus a suitable comparator in the new indication. This trial would be considered as a significant clinical study.

- However, as standard requirements for granting a marketing authorisation for a new indication are applicable, further data including preclinical or clinical pharmacological and further confirmatory clinical trial(s) may also be required for granting a marketing authorisation.

- Exceptionally, other preclinical or clinical studies performed by the applicant could be considered significant if they allowed the use of existing or published data (e.g. clinical trials) to support the marketing authorisation application in the new indication. Significance of these preclinical or clinical studies will be evaluated by the EMEA scientific committees or National Competent Authority on a case-by-case basis. To be considered significant in this situation, preclinical or clinical studies should have been relevant and necessary to the approval of the marketing authorisation application in the sought indication; it is the quality (importance of the data in relation to granting of a marketing authorisation in the new indication), rather than the quantity of the data, which will normally determine the significance of these preclinical or clinical studies.

4. Scientific advice from competent authorities

It is recommended that, in cases of doubt, to request scientific advice from EMEA or National Competent Authorities when designing trials to assess safety and efficacy in a new indication expected to benefit from one-year data exclusivity in accordance with Article 10(5).

Appendix C

Proposal for a Practical early RBA

As the specific benefit of any drug in early development is uncertain, relative risks and odds ratios can't be expressed numerically, making most existing risk benefit models unusable. However, the indication for which the development is planned can indeed be weighted on an unmet medical need scale, which forms the basis for the RBA model described in this chapter. A drug's risk benefit balance (RBB) can then be expressed as the ratio between the weighted Unmet Medical Need (UMN) and the sum of the most relevant weighted risks (W_1 x R_1 – W_n x R_n) multiplied by their frequency of occurrence (F_1 – F_n). If the drug's physic-chemical properties, the planned route of administration and clinical dose predict the absence of significant systemic levels, all risks resulting from systemic bioavailability are nullified. This is accounted for by a separate binary multiplicator (S = 0,1). As the new use of known drugs always precipitates new or unexpected risks (e.g. change in clinical route resulting in side effects at the application site), new risks, albeit unknown have to be factored in as well. The relationship between unmet medical need and the various risks can now be expressed as equation (1):

$$(1)\quad RBB = \frac{WxUMN}{((W_1 \text{ x } R_1 \text{ x } F_1 + W_2 \text{ x } R_2 \text{ x } F_2 \ldots W_n \text{ x } R_n \text{ x } F_n) \text{ x } S) + W_{new} \text{ x } R_{new}}$$

Weighting of the UMN and the individual risks must be carried out using the same numerical scale from 0 to 1 using robust 0.25 increments. For example, repurposing a very hydrophilic drug for a topical application (i.e. S = 0) in a life-threatening indication (W x UMN = 1) would yield the simplified eqation (2):

$$(2)\quad RBB = \frac{1}{W_{new} x R_{new}}$$

Conversely, the repurposing of a drug for subcutaneous injection (S = 1) for a very benign disorder (W x UMN = 0.1) would have to consider all risks and yield equation (3):

$$(3)\quad RBB = \frac{0.1}{((W_1 \text{ x } R_1 \text{ x } F_1 + W_2 \text{ x } R_2 \text{ x } F_2 \ldots W_n \text{ x } R_n \text{ x } F_n) \text{ x } S) + W_{new} \text{ x } R_{new}}$$

Clearly, the RBB for example (3) would normally to be far less positive than (2).

The outcome of any RBA depends on the weighting of the individual risks. For this simple model, weighting of the risks is done in a 3-step process using Multiple Criterion Decision

Analysis (MCDA). First, the level of UMN (W x UMN) must be determined considering both the severity of disease and all existing treatment options. Second, all known risks associated with the use of the drug must be defined as acceptable or unacceptable with a view to the level of UMN. In the presence of unacceptable risks, which cannot likely be eliminated, development should stop. Third, all acceptable risks must be weighted for their clinical severity, again with a view to the level of UMN as moderately adverse drug reactions may be acceptable in treating a serious disease but unacceptable in cosmetic indications.

Using an illustrative example, the assumption is made that Modafinil be developed for the treatment of multiple sclerosis (MS) – related fatigue.[60] Modafinil is indicated for narcolepsy, obstructive sleep apnea and shift work disorder due to its wake-promoting activities similar to sympathomimetics. In a first step, the indication MS – related fatigue needs to be graded on a 0 – 1 scale with 0 for indications that represent no medical needs whatsoever and 1 for life-threatening diseases. Fatigue-like symptoms affect the majority of multiple sclerosis patients and significantly reduce their quality of life.[61] Medical need is clearly warranted and therefore rated 0.5. The next step is to identify unacceptable risks linked to the use of Modafinil. For simplicity, the most current product label (Provigil, Drugs@FDA) is used for this example. No unacceptable risks can be identified, which is not surprising as narcolepsy is not a severe disease that, in this model, would be ranked 0.5 also. Third, all identified risks must be weighted as previously described. Table 3 lists all significant risks (the side effects “thirst” and “taste perversion” were regarded non-significant) and the weighting assigned to each separate one. For the final determination of risk impact, the frequency (F) of each separate risk is multiplied with the weight of that risk. Note that risks easily controlled by dose adjustments (e.g. increased systemic levels in patients with renal of hepatic impairment) are not listed. Risks clearly related to the reference indication (e.g. persistent sleepiness) are not considered either.

Table 3: Calculation of Individual Risk Impact Factors for Modafinil

Identifier	Risk Description	Relative Risk / 100 (F)	W x R	W x R x F
R1	Cytochrome P450 Inhibition (CYP)	1**	0.25	0.25
R2	Serious Rash in Children	0.008	0.75	0.006
R3	Serious Rash in Adults	Rare (< 10^{-4})	0.75	~10^{-4}
R4	Angioedema	Rare (< 10^{-4})	0.75	~10^{-4}
R5	Multi-organ hypersensitivity	Rare (< 10^{-4})	0.75	~ 10^{-4}
R6	Pregnancy category C: Developmental toxicity in rats and rabbits	1**	0.25	0.25
R7	Headache	0.015	0.25	0.004
R8	Back Pain	0.012	0.25	0.003
R9	Flu Syndrome	0.013	0.25	0.003
R10	Chest pain	0.03	0.25	0.008

R11	Chills	0.01*	0.25	0.003
R12	Neck Rigidity	0.01*	0.25	0.003
R13	Hypertension	0.03	0.5	0.015
R14	Tachycardia	0.02	0.5	0.01
R15	Palpitation	0.02	0.25	0.005
R16	Vasodilatation	0.02*	0.25	0.005
R17	Nausea	0.046	0.25	0.012
R18	Diarrhea	0.012	0.25	0.003
R19	Dyspepsia	0.013	0.25	0.003
R20	Dry Mouth	0.02	0.25	0.005
R21	Anorexia	0.04	0.5	0.02
R22	Constipation	0.02	0.25	0.005
R23	Abnormal Liver Function	0.02	0.5	0.01
R24	Flatulence	0.01*	0.25	0.003
R25	Mouth Ulceration	0.01*	0.25	0.003
R26	Eosinophilia	0.01*	0.25	0.003
R27	Edema	0.01*	0.5	0.005
R28	Nervousness	0.023	0.25	0.006
R29	Insomnia	0.05	0.25	0.013
R30	Anxiety	0.05	0.25	0.013
R31	Dizziness	0.013	0.25	0.003
R32	Depression	0.02	0.75	0.015
R33	Paresthesia	0.02*	0.25	0.005
R34	Somnolence	0.02	0.25	0.005
R35	Hypertonia	0.01*	0.5	0.005
R36	Dyskinesia	0.01*	0.5	0.005
R37	Hyperkinesia	0.01*	0.5	0.005
R38	Agitation	0.01*	0.25	0.003
R39	Confusion	0.01*	0.25	0.003
R40	Tremor	0.01*	0.5	0.005
R41	Emotional Lability	0.01*	0.25	0.003
R42	Vertigo	0.01*	0.5	0.005
R43	Rhinitis	0.012	0.25	0.003
R44	Pharyngitis	0.02	0.25	0.005
R45	Lung Disorder	0.02	0.75	0.015
R46	Epistaxis	0.01*	0.25	0.003
R47	Asthma	0.01*	0.5	0.005
R48	Sweating	0.01*	0.25	0.003
R49	Hepes Simplex	0.01*	0.25	0.003
R50	Amblyopia	0.01*	0.75	0.008
R51	Abnormal Vision	0.01*	0.5	0.005
R52	Eye Pain	0.01*	0.25	0.003
R53	Urine Abnormality	0.01*	0.25	0.003
R54	Hematuria	0.01*	0.25	0.003
R55	Pyuria	0.01*	0.25	0.003
R56	Low Abuse Potential (Controlled Substance Act Schedule IV)	1**	0.25	0.25
			Sum	**1.043**

* No events in placebo group

** Properties intrinsic to the drug substance, human data unknown

The sum of all weighted risks multiplied by their frequency yields the value 1.043, which exceeds the level of unmet medical need determined to be 0.5 by about a factor of 2. As both

reference and new indication are assumed to require oral administration, the binary multiplier S equals 1. Inserting these values in equation (1) yields:

$$RBB = \frac{0.5}{1.043 + (W_{new} x R_{new})}$$

If no new risks arise from using Modafinil in multiple sclerosis patients, the estimated RBB will be 0.48. This number is of course meaningless in the absence of an alternative drug or treatment that can be assessed the same way. However, in using this model several key findings were made that are indeed important for the risk benefit evaluation. The sum of all risks exceeds the level of unmet medical need as initially determined and it does so because three major risks contribute nearly 75% of the total risk. The inhibition of cytochrome P 450 enzymes, animal toxicity data and a low potential for drug abuse have been identified as the main risk drivers because they are intrinsically linked to the drug substance. For the repurposing of Modafinil for MS-related fatigue, these risks as well as specific mitigation measures would have to be critically assessed, also with a view to commercial success. If these risks were absent, the total risk would only be half the UMN level and provide for a higher confidence level.

This example shows that the weighting of risks that, when considered separately, do not contribute a large proportion of the total risk is the less critical the lower the frequency of occurrence. Factoring in the frequency therefore adds substantial robustness levering out judgment errors with the exclusion or weighting of risks. Last, this method allows to numerically compare the RBB of any drug to be developed to the RBB of already existing therapies, which could be useful in providing further support in the decision making process.

In spite of these advantages, this model is not without limitations. Most notably, adverse drug reactions from phase 3 trials and post marketing experience are often related to risk factors specific to the target population as the safety databases from use in healthy subjects is usually quite limited. To what extent such risks may be considered requires medical expertise, which could result in the non-applicability of this method in some cases. Second, one important benefit of follow-on treatments when compared to the benchmark can be improved dosing regimens, improved patient convenience or use of an administration route that by itself offers a better risk benefit balance. Conceivably, such improvements may be obvious already in the beginning of a development program potentially off-setting a portion of the total risk. While these factors are not incorporated in this method, they could be evaluated on a cases-by-case basis in a separate step.

In conclusion, this model uses a numerical approach in comparing the level of unmet medical need to the total expected risk of a RLD. While no model is currently capable of yielding a

definitive stop or go answer, this model combines robustness, simplicity and practicality with the most important principles identified by the CHMP (compare chapter 3.1). In addition, it could be easily adjusted as appropriate to the application.

Appendix D

Overview of Regulatory Strategy for the Repurposing of Drugs

Part 1: Decision Tree

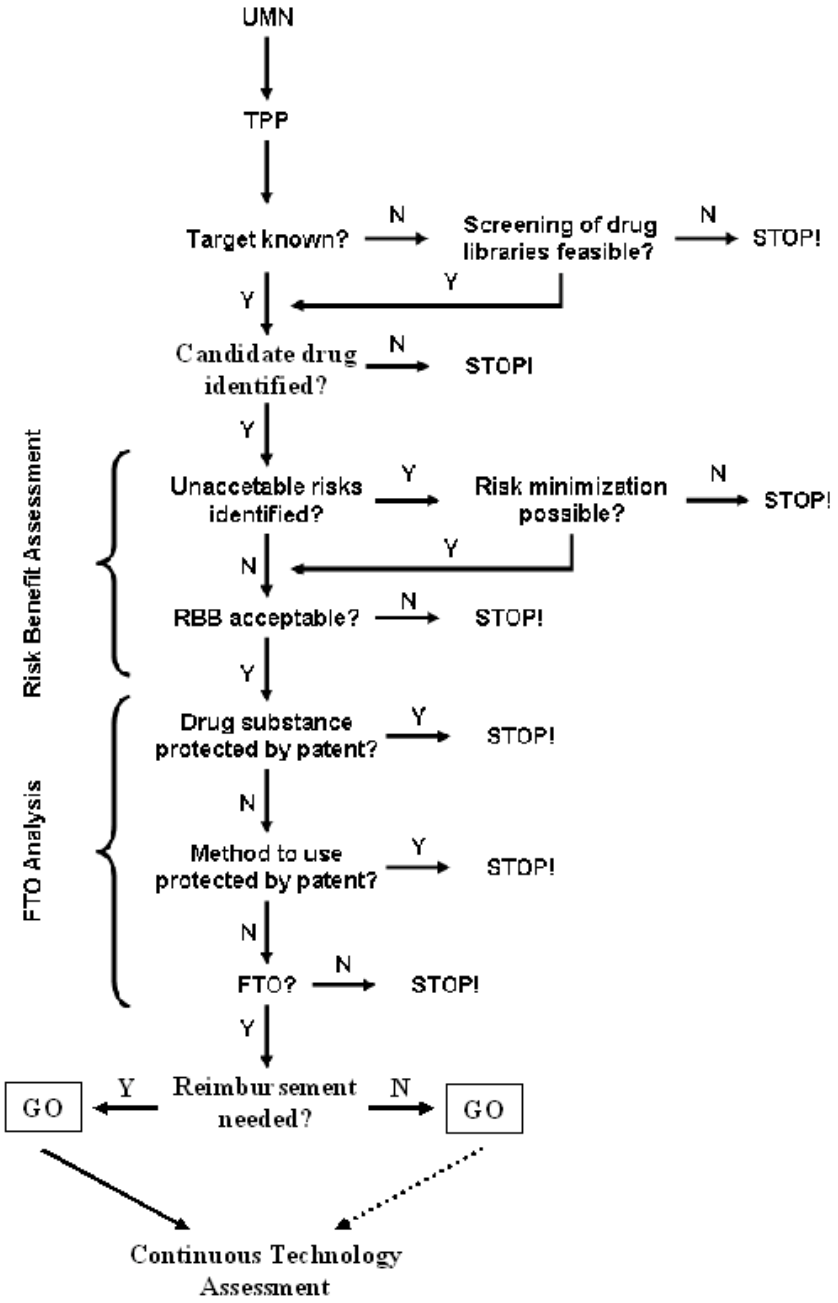


Fig. 7: Drug repurposing decision tree

Part 2: Regulatory Matrix

Table 8: Main variables determining the regulatory repurposing environment in the U.S. and EU

Regulatory Item	RLD previously approved?	Non-Proprietary Studies Available?	Pediatric Indication only?	U.S. Regulatory Requirements	EU Regulatory Requirements
1. Legal basis of application 2. Pediatric requirements 3. Patent term extension 4. Market exclusivity 5. Pediatric incentives	Yes	Yes	Yes	1. 505(b)(2) of FD&C Act 2. Pediatric development plan 3. Likely 4. 3 Years 5. 6 Months	1. PUMA 2. PIP 3. Unlikely 4. 10 Years 5. Included
	Yes	Yes	No	1. 505(b)(2) of FD&C Act 2. Pediatric development plan 3. Likely 4. 3 Years 5. 6 Months	1. MMAA as per Art. 6 and 8(3) of Dir. 2001/83/EC 2. PIP 3. Unlikely 4. 10 Years 5. None
	Yes	No	Yes	1. 505(b)(2) of FD&C Act 2. Pediatric development plan 3. Likely 4. 3 Years 5. 6 Months	1. PUMA 2. PIP 3. Unlikely 4. 10 Years 5. Included
	No	Yes	Yes	1. NME, 505(b)(2) of FD&C Act 2. Pediatric development plan 3. Likely 4. 5 Years 5. 6 Months	1. PUMA 2. PIP 3. Possible 4. 10 Years 5. Included
	Yes	No	No	1. 505(b)(2) of FD&C Act 2. Pediatric development plan 3. Likely 4. 3 Years 5. 6 Months	1. Full dossier as per Art. 6 and 8(3) of Dir. 2001/83/EC 2. PIP 3. Unlikely 4. 10 Years 5. None
	No	Yes	No	1. NME, 505(b)(2) of FD&C Act 2. Pediatric development plan	1. New active substance, MMAA as per Art. 6 and 8(3) of Dir.

				3. Likely 4. 5 Years 5. 6 Months	2001/83/EC 2. PIP 3. Possible 4. 10 Years 5. 6 Months

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.