Pharmaceutical Line Extensions in the United States

A Primer on Definitions and Incentives

Annabelle C. Fowler

Harvard University

October 6, 2017

Abstract

Innovative pharmaceutical companies engage in sophisticated strategies to moderate the loss of revenue they will face when generic competitors enter the market. Known in the industry as product lifecycle management, these strategies often rely on the development and launch of pharmaceutical line extensions. Line extensions are incremental innovations on the product facing generic competition, and usually enter the market with exclusivity periods that outlast those of the original product. The value of line extensions is often debated. Though some line extensions may be associated with clinical benefits to patients such as increased adherence or fewer side effects, critics accuse pharmaceutical companies of developing line extensions to evergreen their patents. This White Paper defines and classifies pharmaceutical line extensions, outlines the supply side incentives that encourage the development of these products in the United States, and introduces methods to identify line extensions in FDA approvals data.

This White Paper was prepared for the NBER-IFS International Network on the Value of Medical Research. I am grateful for support from the National Institute on Aging through grant R24AG058049 to the National Bureau of Economic Research and from the Economic and Social Research Council through grant ES/M008673/1 to the Institute for Fiscal Studies (IFS). Any errors or ambiguities are my own.

1 Introduction

Innovative pharmaceutical companies[1] engage in an inherently risky and often unpredictable research and development (R&D) process to bring new drugs to market (Scott Morton and Kyle, 2011). The cost of bringing a drug to market is high, with estimates ranging from $800 million to $2.6 billion (Dimasi et al., 2016), due to the extensive discovery, pre-clinical and clinical research required. Only about one in one thousand chemical compounds tested are promising enough to file an Investigational New Drug Application to start clinical trials.[2] In 2014, the probability of a drug passing all stages of clinical trials and being approved by the FDA was 11% (DiMasi et al. 2016), yet this figure masks heterogeneity in success rates across different classes of drugs, which vary from 5% to 26% (Mullard, 2016). These figures include both new molecular entities (NMEs), which which are compounds never approved by the FDA, as well as non-NME drugs, such as reformulations and combinations of previously approved drugs. If we exclude non-NMEs, the success rate is about 6% (Mullard, 2016).

Once a drug is available to consumers, it is relatively easy for competing firms to reverse-engineer it and produce it at low cost. Patents and exclusivity periods are two incentives for innovative pharmaceutical firms to invest in R&D to bring drugs to market, as they offer innovative manufacturers a period in which they are protected from competition from cheap imitations (i.e., generics). When patent and exclusivity periods on brand-name pharmaceuticals expire, brand-name drugs experience precipitous drops in sales and revenues, due to generic entry (Ellery and Hansen, 2012). This is often referred to as the patent cliff, and in the pharmaceutical industry, strategies to attenuate this sharp decline in revenue are known as pharmaceutical lifecycle management.

A well-known lifecycle management strategy is the development of a new pharmaceutical

[1] This white paper uses the word innovative to describe pharmaceutical companies that manufacture brand-name products, as opposed to those that manufacture generics.

[2] See The Drug Development and Approval Process, available `http://www.fdareview.org/03_drug_development.php`

product that is based on the drug that is facing generic competition. These new drugs are often referred to as line extensions, reformulations, or follow-on products. Line extensions require less R&D, as the initial discovery and early-stage clinical research of a new molecular entity is not needed. Further, the supply side incentives that encourage innovation via exclusivity periods can often be applied to line extensions. Thus, line extensions are not subject to generic competition at the same time as the original product, but they are often close substitutes to those original products.

Because of the lower costs of R&D and the market protections offered to line extensions, a profit maximizing pharmaceutical firm can strategically introduce line extensions to increase revenue. This strategy is particularly effective if the pharmaceutical company is able to shift volume from the original product to the line extension prior to entry of the generic to the original product. This White Paper focuses on small-molecule drugs (as opposed to biologics), and uses the following terminology:

- **Original Product:** a branded pharmaceutical product that was approved as a new molecular entity (NMEs) by the U.S. Food and Drug Administration (FDA)
- **Line Extension:** a branded pharmaceutical product that (1) includes the same active ingredient (either alone or in combination with other active ingredients) as an original product, (2) is manufactured by the same pharmaceutical company that makes the original product, or by one of its partners or subsidiaries, and (3) is launched after the original product. In the pharmaceutical industry, line extensions may also be referred to as product reformulations or follow-ons.

The value of line extensions can be controversial. Proponents cite the clinical benefits that line extensions provide to patients, such as increased adherence and fewer side effects. However, these benefits may be outweighed by high prices caused by delays in generic entry. Critics

denounce pharmaceutical companies for introducing line extensions that offer little clinical benefit over prior products, but command high prices via patents and exclusivity periods.

Not all line extensions are created equal, and this document provides definitions, foundational knowledge, and evidence that can aid in the research of the value of line extensions. This White Paper is organized as follows. Section 2 defines line extensions and categorizes them based on the ways in which they are distinct from original products. Section 3 explains how secondary patents and market exclusivities apply to line extensions. Finally, Section 4 introduces how to identify line extensions in the drugsatFDA approval database, and outlines some of the brand-name suffixes that are often associated with line extensions.

2 Pharmaceutical Line Extensions

2.1 Line Extensions and Product Lifecycle Management

Line extensions are a pharmaceutical product that are based on a previously approved molecule. They do not require duplication of the R&D that was needed to develop the products active ingredient. Precisely because line extensions have the same active ingredient as an original product, line extensions and original products are typically in the same therapeutic class and are imperfect substitutes. The degree to which line extensions and original products are substitutable varies and discussed in Section 2.2.

Line extensions are part of product lifecycle management strategies when they help the manufacturer of an original product avoid generic competition. Once a generic for an original branded drug enters the market, the manufacturer of the original will see substantial decreases in revenues. Mandatory generic substitution laws in the United States mean that after entry, generics capture most of an original products volume.

The manufacturer of an original product may pre-empt this by launching a line extension. If

the pharmaceutical company is able to shift volume from its original drug to the line extension before the generic to the original product enters, the volume that shifted to the line extension would be insulated from generic competition. Pharmaceutical companies shift volume to line extensions via marketing, pricing, and negotiations with PBMs and other managed care entities.

In the United States, generics are defined as pharmaceutical equivalents to a branded pharmaceutical product. A product must meet three criteria for the FDA to deem it a pharmaceutical equivalent of another product: (1) both products must have the same active ingredients, (2) both must have the same dosage form and route of administration, (3) and both must have identical concentrations or strength of the active ingredient.[3] By definition, a line extension is not a pharmaceutical equivalent to an original product, and it follows that the generic of an original product is not a generic for a line extension.

Some line extensions may provide clinical benefits beyond their original products. For instance, some extended release medications are associated with increased adherence, fewer patient side effects, and better absorption (Shargel et al. 2016). However, the value of line extension is debated. Critics of the practice refer to it as product hopping or evergreening, and characterize line extensions as strategic products that extend an active molecules market protections, raising prices without commensurate clinical benefits. In a textbook on generic entry and pharmaceutical life, Voet (2005) quotes a Federal Trade Commission officer, who referred to product lifecycle management as the practice of "introducing new patented products with minor or no substantive improvements in the hopes of preventing substitution to lower priced generics."

[3]See the FDA Glossary of Terms, available at `https://www.fda.gov/drugs/informationondrugs/ucm079436.htm`

2.2 Types of Line Extensions

There are several types of line extensions that a pharmaceutical company can develop. Below, I categorize and define the most common types, and explain how each type relates to original products. Though the types of line extensions described are listed roughly in increasing order of chemical difference from the original molecule, this is not a rigid typology. There is variation in how close of a substitute a line extension is to an original product both within and across the categories below.

2.2.1 Dosage or formulation changes

A line extension may have the same active ingredient as an original product but differ in dosage or formulation. The FDA defines a pharmaceuticals formulation as two components: route of administration (e.g., oral) and an administration form (e.g., tablets).[4] The dosage or strength of a pharmaceutical refers to the amount of active ingredient it contains (e.g., milligrams of active ingredient per pill).

Line extensions of this type may differ from an original product in administration and/or dosage.[5] A common example of a line extension of this type is an extended-release formulation, which changes an original products dosage and administration form. Line extensions that only change route of administration or dosage are often alleged to add little clinical value;[6] however, some dosage or administration changes can make a drug more suitable for certain patients over original product.[7] Examples of original products and line extensions by dosage or formulation change follow.

[4]Descriptions of all FDA recognized dosage forms are available at `https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/datastandardsmanualmonographs/ucm071666.htm`

[5]For instance, a line extension may differ from an original product in administration form but not route of administration or dosage (see Asacol and Delzicol), or in both dosage and formulation (see Abilify and Abilify Maintena), or in dosage but not formulation (see Aricept and Aricept 23).

[6]Line extensions Aricept 23 and Delzicol are examples. Introduction of both these products was controversial.

[7]Line extension Aricept ODT dissolves orally, for patients with trouble swallowing. Similarly, unlike original product Abilify, line extension Abilify Maintena is an injection that can be used to stabilize patients in a crisis.

Aricept, Aricept ODT, and Aricept 23

Manufacturer: Eisai, Inc. in collaboration with Pfizer

Active ingredient: donepezil

- **Original Product:** Aricept, an oral tablet of 5 mg or 10 mg, approved to treat Alzheimers Disease in November 1996
- **Line Extension:** Aricept ODT, an orally disintegrating tablet of 5 mg or 10 mg, approved to treat Alzheimers Disease in October 2004
- **Line Extension:** Aricept 23, an oral tablet of 23 mg, approved to treat Alzheimers Disease in July 2010

Namenda and Namenda XR

Manufacturer: Forest Labs

Active ingredient: memantine

- **Original Product:** Namenda, an oral tablet of 5 mg or 10 mg, approved to treat Alzheimers Disease in October 2003
- **Line Extension:** Namenda XR, an oral extended-release capsule of 7 mg, 14 mg, 21 mg or 28 mg, approved to treat Alzheimers Disease in June 2010

Asacol, Asacol HD, and Delzicol

Manufacturer: Apil

Active ingredient: mesalamine

- **Original Product:** Asacol, an oral delayed-release tablet of 400 mg, approved to treat ulcerative colitis in January 1992

- **Line Extension:** Asacol HD, an oral delayed-release tablet of 800 mg, approved to treat ulcerative colitis in May 2008
- **Line Extension:** Delzicol, an oral delayed-release capsule of 400 mg, approved to treat ulcerative colitis in February 2013

Abilify and Abilify Maintena

Manufacturer: Otsuka

Active ingredient: aripiprazole

- **Original Product:** Abilify, an oral tablet of 2 mg, 5 mg, 10 mg, 15 mg, 20 mg or 30 mg, approved as an antipsychotic in November 2002
- **Line Extension:** Abilify Maintena, an intramuscular extended-release suspension of 300 mg or 400 mg, approved as an antipsychotic in February 2013

2.2.2 Combination Products

Fixed dose combination drugs are line extensions that combine an original product and another active ingredient in the same dosage form. There are other fixed dose combination products that combine two active ingredients that are off-patent, but those do not count as line extensions as defined in this paper. To be a line extension as defined above, one of the active ingredients of a fixed dose combination must be the same as that of an original product that was developed by the same manufacturer. The other active ingredient may be branded or generic.

Fixed combination drugs are anecdotally said to increase adherence by reducing the number of individual medications a patient takes. However, the literature on whether there is a benefit

in adherence is mixed, and many studies are based on non-random allocation of patients to medications. One study that worked around this problem used patient propensity score matching and found that taking a fixed dose combination of metformin and sulfonylurea instead of both medications separately increased adherence by 13% (Pan et al. 2008). However, if the clinical benefit of increases in adherence are small, and adherence only increases by a few percentage points, the value of fixed dose combinations is perhaps not worth the high cost that the line extension will have due to exclusivity and patent protections. Fixed drug combinations may also give prescribers less flexibility with the doses of each component. Examples of fixed dose combinations follow.

Januvia and Janumet

Manufacturer: Merck

The active ingredient in Januvia is sitagliptin. Janumet is a fixed dose combination of Januvia and metformin, a generic often considered the first-line treatment for type 2 diabetes.

- **Original Product:**Januvia, an oral tablet of 25 mg, 50 mg, or 100 mg, approved to treat type 2 diabetes in October 2006
- **Line Extension:** Janumet, a fixed dose combination oral tablet of 50 mg sitagliptin/500 mg metformin or 50 mg sitagliptin/1000 mg metformin, approved to treat type 2 diabetes in March 2007

Norvasc, Lipitor and Caduet

Manufacturer: Pfizer

The active ingredient in Norvasc is amlodipine besylate, and the active ingredient in Lipitor is atorvastatin. Caduet is a fixed dose combination of Norvasc and Lipitor.

- **Original Product:** Norvasc, an oral tablet of 2.5 mg, 5 mg and 10 mg, approved to treat hypertension in July 1992
- **Original Product:** Lipitor, an oral tablet of 10 mg, 20 mg, 40 mg and 80 mg, approved to lower cholesterol in December 1996
- **Line Extension:** Caduet, a fixed dose combination oral tablet of amlodipine besylate/atorvastatin in 5/10 mg, 10/10 mg, 5/20 mg, 10/20 mg, 5/40 mg, 10/40 mg, 5/80 mg and 10/80 mg, approved for cardiovascular disease in January 2004

2.2.3 Enantiomers

The molecules in a chemical compound can often exist in a number of structural configurations, called isomers. An isomer has the same molecular formula of another chemical compounds, but the bonds between the components may be different. A special type of isomer is an enantiomer, which has the same connections between components but is a flipped or rotated version of the chemical compound, and not a superimposable mirror image of it. Chemical compounds with enantiomers are called chiral molecules, and enantiomers can be left-handed (S-enantiomer) or right-handed (R-enantiomer).

A racemic mixture is a chemical compound that is made up of the same number of S- and R-enantiomers of a molecule. A racemic switch or chiral switch occurs when a pharmaceutical company takes an original product that is a racemic mixture, and strips it of one of its enantiomers, leaving a purified single enantiomer.

Enantiomers do not necessarily have the same chemical properties as the original chemical compound, and as such they may offer clinical advantages to patients. Gellad and colleagues (2014) studied the nine single-enantiomer products approved by the FDA from 2001 to 2011. Three of those had a clinical trial that compared the single enantiomer to the racemic mixture,

but there was no evidence that the single enantiomers were clinically superior. Other studies also suggest limited evidence of clinical superiority,[8] however, a study in the antidepressant class by Huskamp and coauthors (2009) found that Lexapro, the S-entantiomer of Celexa, was associated with decreased probability of discontinuation versus Celexa. Below are two examples of original products and enantiomer line extensions, including Celexa and Lexapro:

Celexa and Lexapro

Manufacturer: Forest Labs

Lexapro is an enantiomer of Celexa and has different pharmaceutical properties. Celexas active ingredient is citalopram hydrobomide, and Lexapros active ingredient is escitalopram oxalate

- **Original Product:** Celexa, an oral tablet of 10 mg, 20 mg, 30 mg, or 60 mg (discontinued), approved as a treatment for depression in July 1998
- **Line Extension:** Lexapro, an oral tablet of 5 mg, 10 mg or 20 mg, approved as a treatment for major depressive disorder in August 2002

Prilosec and Nexium

Manufacturer: AstraZeneca

Prilosec was a racemic mixture, and Nexium the S-entantiomer of that mixture. Prilosec was discontinued and an over-the-counter version released in June 2003. Prilosecs active ingredient is omeprazole and Nexiums active ingredient is esomeprazole

- **Original Product:** Prilosec, a delayed release capsule of 10 mg, 20 mg, or 40 mg, approved as a proton pump inhibitor in September 1989
- **Line Extension:** Nexium, a delayed release capsule of 20 mg or 40 mg, approved as a proton pump inhibitor in February 2001

[8]See Therapeutics Initiative, 2002 `http://www.ti.ubc.ca/PDF/45.pdf`

3 Supply-side Incentives for Line Extensions

Line extensions are often awarded market protections, and do not face generic competition as imminently as their original products. Because line extensions are not subject to competition by the generics to an original formulation, line extensions are in effect able to extend the exclusive marketing period for a given active ingredient or chemical compound. To the extent that patients switch from an original formulation to a line extension, pharmaceutical companies are able to retain some of those revenues which would otherwise have been lost to generic competition. The strategy can be effective: Huskamp et al (2008) examine pharmaceutical company strategies to extend market exclusivities on drugs in the serotonin reuptake inhibitor (SSRI) class that are nearing generic competition. In the period from 1997 through 2004, they find that introducing product reformulations and attempting to shift demand from original products to these reformulations via a shift of promotional dollars to these new products prior to generic entry, such as Prozac Weekly (a once-weekly formulation of Prozac), Paxil CR (a controlled-release version of Paxil), and Lexapro (an enantiomer of Celexa), is a common strategy.

As described above, periods of market exclusivity exist to incentivize innovation. There are two types of market exclusivities that apply to all pharmaceuticals, patent exclusivity and regulatory or data exclusivity. Most of the literature has focused on the patents and regulatory exclusivities granted to original drugs. This section highlights the protections available to line extensions, and discusses them with regard to those granted to original products.

3.1 Secondary Patents

In the United States, a novel and nonobvious invention may be granted a patent by the USPTO. Patents award an inventor a monopoly of 20 years from the date of filing. In the pharmaceutical industry, patents are usually filed when a molecule appears to be viable, prior to the pre-clinical

or clinical trial stages of R&D. (Ellery and Hansen, 2012). This patent usually covers an active chemical compound and small variations (such as its salts and esters), and is known as a composition of matter patent, a compound patent or a primary patent. An original pharmaceutical product will virtually always have one.

Because the 20-year patent clock starts running prior to submission of a New Drug Application (NDA) to the FDA, and because the FDA takes time to review the NDA and approve the drug, the effective life of a primary patent is much shorter.[9] Van Norman (2016) describes an average of 7 to 12 years from pre-clinical testing to FDA approval.

A pharmaceutical company may also file for patents that cover other attributes of pharmaceutical products. These patents are called secondary because they are usually filed after the compound patent. These secondary patents may cover modified forms, other medical uses, combinations, formulations, dosages, etc. of a given molecular entity. The number of secondary patents is increasing, with the vast majority of patents on pharmaceutical products now secondary (Ellery and Hansen, 2012). Both original drugs and line extensions may have secondary patents. Primary patents may also include claims that cover secondary features.

Because line extensions are based on the active ingredient of an original product, they are often protected by original products primary patent. Thus, any secondary patent on a line extension may protect it from competition beyond the original drugs primary patent.

Beyond the base molecule, a patent may be for medical use (but easier for a competitor to get around), or for a specific formulation. Secondary patents for formulations or composition often include the non-active ingredients with which the active ingredient is combined. And many other things can be patented as well to grow and protect a brand. Sometimes patent extra stuff that expire later. Might cover methods of manufacturing drug or something more.

[9]One of the provisions of the Hatch-Waxman Act allows pharmaceutical companies to recoup some lost patent trials during R&D. The maximum extension is 5 years, but maximum patent time remaining after approval cannot exceed 14 years. Only one patent that covers each drug can be extended. Thus, Hatch-Waxman patent extension rarely applies to line extensions.

Even if a primary patent has expired, secondary patents may discourage generic entry via strategic litigation (Correa, 2007), which means that an innovative pharmaceutical company may allege infringement, and courts may grant injunctions that block generic entry.

Much of the literature has focused on primary patents, related to the original chemical compound, secondary patents are common and can extend the monopoly period of drugs. Hao et al. 2015 examine the effective patent life of fixed drug combinations approved by the FDA from 1980 to 2012. For manufacturers who developed the original product as well as the fixed dose combination, the combination added a median of at least 7.73 years to the active ingredients effective patent and market exclusivity periods.

One study by Kapcynski, Park and Sampat (2012) examines the prevalence of secondary patents associated with all new molecular entities approved in the United States from 1988 to 2005. They classified the claims in patents into primary (covering active chemical compounds), and secondary (formulations, method of treatment or use, and polymorph, isomer, prodrug, ester or salts patents). They did not focus on combination drugs or other line extensions as defined in this paper. Find that 56% of the drugs have at least one independent secondary patent on formulation, 24% on PIPES, and 63% on method of use. They find that if an NME has a primary patent, independent secondary patents adds 4 to 5 years of exclusivity. NMEs without primary patent receive on average 9 to 11 additional years of exclusivity from independent secondary patents. Furthermore, whereas 11% of primary patents are issued post FDA approval of a drug, just under half of secondary patents are issued post approval, and 1 in 5 are filed post approval. This suggests there is strategic filing of secondary patents, even in original products. The authors also state that line extensions are less likely to have chemical compound patents, and thus are more reliant on secondary patents.

3.1.1 Risks of Secondary Patents

Secondary patents may be weaker than primary patents because they may be less nonobvious given the prior art. In October 2007, the USPTO published Examination Guidelines for Determining Obviousness,[10] which changed the extent to which certain inventions could be patentable. Specifically, combining prior art elements according to known methods to yield predictable results was no longer a patentable innovation. The implication of these guidelines is that certain combination therapies would no longer be patentable. Further provisions deemed extended release and dosages switches less nonobvious than they were previously, and as such they are not as patentable. Enantiomers are also now less patentable. If a racemic mixture had been previously patented, then a pure enantiomer from the racemic mixture is part of the prior art. For fixed-dose combinations, the USPTO may grant a patent if the combination is innovative, different from the prior art with unpredictable results and unexpected clinical outcomes of the combination, and with useful or meaningful health effects (Hao et al. 2015).

Work has shown that secondary patents that generate more patent life are more likely to be challenged in the United States (Hemphill and Sampat 2012), yet the process of challenging a patent is still time consuming and not a guarantee the patent will be invalidated. In addition, secondary patents that are listed in the FDAs Orange Book can preclude the FDA from approving generic drugs (Sokal and Gerstenblith, 2010).

Secondary patents are sometimes critiqued for lacking true inventiveness and non-obviousness, and as such they are often easier to challenge and can be designed around. In a report for the World Health Organization, Carlos Correa (2007) argues that certain secondary patents lack an inventive step necessary for patentability, and recommends that innovations that seek secondary patents ought to be deemed obvious unless they offer a truly unexpected effect or great clinical advantage compared to the prior art.

[10]See `https://www.uspto.gov/sites/default/files/web/offices/com/sol/notices/72fr57526.pdf`

In summary, patent strategy is very complex as drugs covered by many patents, with some easier to challenge than others. Secondary patents can be used to add exclusive marketing time to line extensions. Importantly, the later a secondary patent is filed, the longer the monopoly period will run, provided the patent holds up. However, the attributes covered by secondary patents are being deemed less novel and as such are less patentable and easier to challenge.

3.2 FDA Data Exclusivities

The Hatch-Waxman Act, signed into law in 1984, created a streamlined process for the approval of generic pharmaceuticals and implemented new incentives for the development of branded pharmaceuticals. A provision of the Act allowed generic companies to file abbreviated new drug applications (ANDAs), which did not require the duplication of clinical trials to demonstrate safety and efficacy; instead, generic manufacturers had to show that their proposed generic was both bioequivalent and a pharmaceutical equivalent of the reference drug product.

To incentivize innovation, the Hatch-Waxman Act created periods of data exclusivity for certain branded pharmaceuticals, which the FDA gives to innovative pharmaceutical companies by the when an NDA is approved. Unlike patents, data exclusivities cannot be challenged in court, but similarly to patents, they prevent generic entry for a certain number of years. Innovative pharmaceutical companies do not need to apply for data exclusivity. Instead, the FDAs Center for Drug Research and Evaluation (CDER) automatically determines exclusivity for all NDAs.

Exclusivities run concurrently with patents, which means that if a patent is deemed invalid, a branded drug product may still be protected from generic entry under FDA exclusivity. To be precise, the Hatch-Waxman exclusivity periods are data exclusivity, which means that during the period, generic companies are barred from accessing the clinical and pharmaceutical data that would facilitate the submission of their ANDAs. However, in the absence of a patent, if

a generic company is able to generate its own data and run clinical trials, it could in theory submit an NDA for its product.

There are two types of FDA data exclusivities that can apply to Line Extensions: New Chemical Entity Exclusivity and New Clinical Investigation Exclusivity, summarized below:

- **New Chemical Entity (NCE) Exclusivity:** Also known as new drug product exclusivity, this period runs for five years from the NDA approval of a product that contains an NME never before approved by the FDA in any form.[11] During NCE exclusivity, the FDA cannot accept ANDA submissions, with the exception of an ANDA that contains a paragraph IV challenge to one of the patents of the reference drug. In this case, the FDA can accept the ANDA after four years instead of five.[12] However, because the FDA review process takes time, the effective protection provided by new chemical entity exclusivity is generally six years or more (Kesselheim et al. 2017).

- **New Clinical Investigation Exclusivity:** This exclusivity runs for three years, and applies to drug products that required new clinical investigations. A new clinical investigation must be human research and not duplicative of another drugs trials that were used to determine safety and effectiveness. Typically, these trials will involve a dosage strength or form switch, a new patient population, or a new indication. During the three years of new clinical investigation exclusivity, the FDA may accept ANDA submissions but cannot approve them. However, these may be approved once exclusivity ends at three years. Finally, new clinical investigation exclusivity only covers the particular formulation, population or indication studied in the trial (Ellery and Hansen, 2012).

[11] The interpretation of this statute has changed. This is discussed later in this White Paper.

[12] For more detail, see the FDAs Small Business Assistance: Frequently Ask Questions for New Drug Product Exclusivity, available at `https://www.fda.gov/drugs/developmentapprovalprocess/smallbusinessassistance/ucm069962.htm`

3.2.1 Exclusivity Periods and Line Extensions

Most line extensions that involve dosage form changes get three-year new clinical investigation exclusivity. For combination drugs, the exclusivity period has changed over the past years. The provisions for the five-year new chemical entity exclusivity stated that it applied to a drug with a NME never before approved by the FDA. As a result, the FDA deemed any fixed-combination drug that contained a previously approved chemical compound ineligible for five-year NCE exclusivity, even if one of the chemical compounds was new.[13] In July 2013, Bayer petitioned the FDA to reconsider the interpretation. Bayer had introduced Natazia, a fixed dose combination of birth control, which combined estradiol valerate (a generic), and dienogest (a never before approved active ingredient). Natazia was granted three years of exclusivity, instead of five.[14] In October 2014, the FDA issued new guidance announcing they had revised their interpretation of the NCE exclusivity provisions to grant five years NCE exclusivity to fixed-dose combinations as long as one of the chemical compounds is new. The decision did not apply retroactively to Bayers Natazia, but has since applied to drugs such as Gileads Harvoni, a combination of sofosbuvir and ledipasvir used to treat Hepatitis C.[15]

The exclusivity periods for enantiomers have also changed. Following the Hatch-Waxman Act, enantiomers were not awarded five-year new chemical entity exclusivity.[16] However, the FDA Revitalization Act of 2007 allowed for certain single enantiomers to receive five year exclusivity as a new chemical entity. Concerned with potential evergreening, Congress deemed this was only for enantiomers that had a new use and did not rely on studies used to get a

[13]See `https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm386685.pdf`

[14]See Gaffney, A. Bayer: FDAs Exclusivity Provisions for Fixed-Dose Combinations Illegal, Should be Longer, July 24, 2013. Regulatory Affairs Professionals Society, available `http://www.raps.org/regulatoryDetail.aspx?id=9210`

[15]See The prior approval of a drug containing an active ingredient of the innovator drug is not necessarily a death knell for NCE exclusivity, September 7, 2016 available `https://www.law360.com/articles/836524/fda-is-evolving-on-qualifications-for-new-chemical-entity-`

[16]The preamble of the FDAs July 1989 proposed regulations regarding Hatch-Waxman specifically said that single enantiomer of a previously approved racemate contains a previously approved active moiety and is therefore not considered a new chemical entity

previous racemic mixture approved (Sullivan, 2008). An additional condition is that if the FDA has approved a racemic mixture with NCE exclusivity, then an enantiomer will only be approved for use in the same therapeutic category ten years after the enantiomers approval. The first enantiomer to be awarded five year exclusivity under this provision was the antidepressant Fetzima (levomilnacipran) in July 2013.[17]

In sum, in the United States the FDA provides line extensions between three to five years of data exclusivity. There is variation across countries on exclusivity periods for products that require additional clinical trials. For instance, the EU awards no exclusivities for new route of administration or new formulation, but does award one year for new indications.[18] In Japan, new routes of administration, new formulations and new indications get four to six years of exclusivity (Ellery and Hansen, 2012).

4 Identifying Line Extensions

This section outlines methods for researchers to identify line extensions in FDA data.

4.1 By FDA approval classification

The drugsatFDA database includes application information for all approved FDA drugs. The CDER assigns each NDA a classification code, which categorizes NDAs based on characteristics including their relationship to existing products.[19] Importantly, these classification codes do not indicate the type of exclusivity a drug was granted, or how innovative or valuable the drug is relative to other products. Codes are assigned at NDA filing and then reassessed when an

[17]See The prior approval of a drug containing an active ingredient of the innovator drug is not necessarily a death knell for NCE exclusivity, September 7, 2016 available `https://www.law360.com/articles/836524/fda-is-evolving-on-qualifications-for-new-chemical-entity-`

[18]In the United States, new indications often are awarded the 3 year new clinical investigation exclusivity

[19]See Manual of Policies and Procedures, Center for Drug Evaluation and Research, MAPP 5018.2, NDA Classification Codes, effective November 4, 2015. Available at `https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm470773.pdf`

NDA is approved. Only one code may be assigned, with the exception of combination products which may have two.

Original products as defined in this white paper are assigned chemical code Type 1, which corresponds to NMEs. Per FDA guidance, drugs approved as an NME contain no active moiety previously approved by the FDA or previously marketed as a drug in the USA. There are 10 codes in total,[20] and some of them may indicate that a product is a line extension. As a rule of thumb, if the manufacturer of an original product or one of its subsidiaries files an NDA or a supplemental NDA that is assigned one of the following chemical type codes, the product is a line extension to the original:

Type 2: New Active Ingredient

Assigned to products with new active ingredients that are not NMEs. This may include active ingredients that are single enantiomers if a racemic mixture with that enantiomer had been previously approved, or vice versa. Further, Type 2 includes products with an ester, salt or noncovalent derivative of an NME that has not been approved before or marketed in the US.

Type 3: New Dosage Form

This type is assigned to new dosage forms for a previously approved NME. The indication of the drug need not be the same as the original product. Type 3 includes changes to the active and inactive ingredients in a dose of the drug product. This may include the appearance of the drug, the physical form of the drug product prior to dispensing, the route of administration, and the features that affect frequency of dosing.

[20]This white paper describes the subset of codes that can be used to identify products as line extensions. The codes not mentioned above are: Type 7 (previously marketed without approved NDA), Type 8 (RX to OTC switch), and Types 6, 9 and 10 (New indications or claims). For detail, see Manual of Policies and Procedures, Center for Drug Evaluation and Research, MAPP 5018.2, NDA Classification Codes, effective November 4, 2015. Available at `https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm470773.pdf`

Type 4: New Combination

Type 4 is assigned to a drug with two or more active ingredients combined into a single dosage form of a product, or two or more products packaged together under one label. These products can have more than one classification code, such as Type 1,4, or Type 2,4, if one of the active ingredients is either Type 1 or Type 2.

Type 5: New Formulation or Other Differences

Type 5 may be assigned to a variety of products, including changes in formulation, but also in indication, applicant or manufacturer. For example, if a manufacturer changes the inactive ingredients in a product and submits a new NDA (rather than a supplement), then the drug is approved as Type 5. Type 5 also corresponds to active ingredients previously approved only as combination drugs. To use Type 5 to identify line extensions, the Type 5 product must be manufactured by the same manufacturer or applicant as an original product.

4.2 Orange Book Data

All NDAs must include patent information, which the FDA publishes in the list of Approved Drug Products with Therapeutic Equivalence Evaluations, or Orange Book. The Orange book does not include patents beyond the scope of the FDA, such as process or manufacturing patents.[21] Though the online Orange Book only lists the patents and exclusivity periods that have not yet expired, an Orange Book dataset that goes back in time (such as the Orange Book data at the NBER) includes the patent and exclusivity associated with each drug product, as well as expiration dates. This can be used to narrow down products with three-year exclusivity.

[21] See Patents and Exclusivity, available at `https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm447307.pdf`

4.3 By Product Suffix or Name

Pharmaceuticals may have brand names with suffixes or words that suggest the product is a line extension or has a line extension. These are usually due to reformulation or a change in dosage strength (rather than as combinations or other enantiomer). Examples follow:

- CD (controlled delivery)
- CR (controlled release)
- DR (delayed release)
- ER (extended release)
- ES (extra strength)
- IR (immediate release)
- LA (long-acting)
- LAR (long-acting release)
- MR (modified release)
- ODT (orally disintegrating tablet)
- PR (prolonged release)
- SA (sustained action)
- SR (sustained release)
- TR (timed release)
- XL (extended release)
- XR (extended release)
- XS (extra strength)
- XT (extended release)
- Modified (delayed or targeted release)
- Sustained (controlled, constant release)
- Target (targets a given part of the body)
- Weekly (dosage is once per week)

References

[1] Carlos María Correa et al. *Guidelines for the examination of pharmaceutical patents: developing a public health perspective.* ICTSD, 2007.

[2] Jonathan J. Darrow. The patentability of enantiomers: Implications for the pharmaceutical industry. *Stanford Technology Law Review*, 2007:2–3, January 2007.

[3] Joseph A. Dimasi, Henry G. Grabowski, and Ronald W. Hansen. Innovation in the pharmaceutical industry: New estimates of r&d costs. *Journal of Health Economics*, 47:20–33, May 2016.

[4] Tony Ellery. *Pharmaceutical lifecycle management : making the most of each and every brand.* John Wiley & Sons, Hoboken, N.J., 2012.

[5] Walid F Gellad, Phillip Choi, Margaret Mizah, Chester B Good, and Aaron S Kesselheim. Assessing the chiral switch: approval and use of single-enantiomer drugs, 2001 to 2011. *The American journal of managed care*, 20(3), March 2014.

[6] Jing Hao, Rosa Rodriguez-Monguio, and Enrique Seoane-Vazquez. Fixed-dose combination drug approvals, patents and market exclusivities compared to single active ingredient pharmaceuticals.(report). *PLoS ONE*, 10(10), October 2015.

[7] C. Scott Hemphill and Bhaven N. Sampat. Evergreening, patent challenges, and effective market life in pharmaceuticals. *Journal of Health Economics*, 31(2):327–339, March 2012.

[8] Haiden A Huskamp, Alisa B Busch, Marisa E Domino, and Sharon-Lise T Normand. Antidepressant reformulations: who uses them, and what are the benefits? *Health affairs (Project Hope)*, 28(3), 2009.

[9] Haiden A. Huskamp, Julie M. Donohue, Catherine Koss, Ernst R. Berndt, and Richard G. Frank. Generic entry, reformulations and promotion of ssris in the us. *PharmacoEconomics*, 26(7):603–616, Jul 2008.

[10] Amy Kapczynski, Chan Park, and Bhaven Sampat. Polymorphs and prodrugs and salts (oh my!): An empirical analysis of secondary pharmaceutical patents. *PLOS ONE*, 7(12):1–9, 12 2012.

[11] Aaron S. Kesselheim, Michael S. Sinha, and Jerry Avorn. Determinants of market exclusivity for prescription drugs in the united states. *JAMA Internal Medicine*, September 2017.

[12] Fiona Scott Morton and Margaret Kyle. Chapter twelve - markets for pharmaceutical products. In Thomas G. Mcguire Mark V. Pauly and Pedro P. Barros, editors, *Handbook of Health Economics*, volume 2 of *Handbook of Health Economics*, pages 763 – 823. Elsevier, 2011.

[13] Asher Mullard. Parsing clinical success rates. *Nature Reviews Drug Discovery*, 15(7), June 2016.

[14] Susana Murteira, Aurlie Millier, Zied Ghezaiel, and Michel Lamure. Drug reformulations and repositioning in the pharmaceutical industry and their impact on market access: regulatory implications. *Journal of market access & health policy*, 2, 2014.

[15] Leon Shargel, Andrew B. C Yu, and Susanna Wu-Pong. *Applied biopharmaceutics & pharmacokinetics*. McGraw-Hill's AccessPharmacy. McGraw-Hill Education LLC, New York, N.Y, 6th ed. edition, 2012.

[16] Allen M. Sokal and Bart A. Gerstenblith. The hatch-waxman act: Encouraging innovation and generic drug competition. *Current Topics in Medicinal Chemistry*, 10(18):1950–1959, 2010.

[17] Martin A Voet. *The generic challenge : understanding patents, FDA and pharmaceutical life-cycle management*. BrownWalker Press, Boca Raton, Fla., 2005.