

GILBERT'S

December 23, 2002

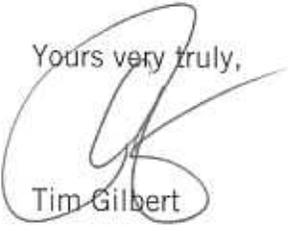
Via Electronic Comment Submission Form and Email

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD
20852

Dear Sir or Madam:

Re: Written comments of Apotex Corp. on Applications for FDA Approval to Market a New Drug: Patent Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug is Invalid or Will Not be Infringed (Docket No. 02N-0417)

Attached please find the written comments of Apotex Corp. in response to the Food and Drug Administration's Proposed Rules (Docket No. 02N-0417) published in the Federal Register Vol. 67, No. 206 on Thursday, October 24, 2002.

Yours very truly,

Tim Gilbert

TG:tm
Encl.

cc: Dr. Mark McClellan, Commissioner, FDA
Daniel Troy, Chief Counsel, FDA

Comments on FDA's Proposed Rules Regarding Patent Listings and 30-Month Stays

Food and Drug Administration

December 23, 2002 | Rockville, Maryland

COMMENTS OF



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EXECUTIVE SUMMARY AND KEY RECOMMENDATIONS

Apotex Corp. (“Apotex”) welcomes the Food and Drug Administration’s (“FDA”) initiative in proposing new regulations (“Proposed Rules”) that seek to address abuses of the Hatch-Waxman Act (“the Act” or “statute”).¹

While Apotex supports the policy objectives in restricting NDA holders to one 30-month stay of generic approval, Apotex is concerned with a variety of provisions in the Proposed Rules. The Proposed Rules significantly expand the types of patents eligible for listing in the Orange Book and potentially create undesirable consequences that may delay generic entry. Apotex recommends that FDA not allow patents on different forms of a drug to be listed, nor product-by-process patents that claim old drug products.

The expansion of the types of patents eligible for listing in the Orange Book is not in accordance with the Act. While the agency has discretion to interpret its own enabling statute, it cannot act contrary to the specific statutory language.² Even if the agency does have room to adopt a wider listing policy, this policy would not be in the public interest. The expansion of patent listings will lead to increased litigation, increased costs of generic entry and delayed generic approvals. Consumers, governments and third-party payors lack an adequate remedy to compensate them for the increased drug prices paid as a result of delayed generic entry. As discussed more fully below, the expansion of patent listings represents an opportunity for additional periods of 180-day exclusivity that could delay generic entry for years.

As for the Proposed Rule’s 30-month stay provision, Apotex believes that any change to the regulations limiting the potential number of 30-month stays will be welcome. Nevertheless, some significant questions remain unanswered and require clarification. While the agency would not require the notification of paragraph IV certifications to NDA holders with respect to later issued and listed patents, the agency does not address what occurs when a notice is provided because the generic seeks to obtain voluntary pre-approval litigation of patent invalidity or infringement issues.

Further, although not addressed in the Proposed Rules, the statute also arguably contains timing restrictions on the eligibility of patents for listing in the Orange Book which would limit the number of patents that generic applicants would need to address when submitting an ANDA. This would practically have the effect of limiting generic applicants to having one 30-month stay of approval and also prevent later-issued patents from preventing generic entry by reason of the 180-day exclusivity provision. There are also other approaches to the listing eligibility and requirements

¹ We acknowledge the significant contribution of the following to the preparation of this document: Hugh Moore and Bill Rakoczy, Lord Bissell & Brook; Arthur Tsien, Olsson Frank and Weeda, P.C.; Professor David J. Bederman, Emory University School of Law.

² *Chevron v. Natural Resources Defense Council*, 467 U.S. 837 (1984).

EXECUTIVE SUMMARY AND KEY RECOMMENDATIONS

to comply that merit consideration by the agency. Apotex urges FDA to consider these alternative regulatory means to limit successive 30-month stays.

Apotex supports the agency's initiative in addressing the abuses of Hatch-Waxman. Apotex recommends as follows:

1. The patent eligibility criteria should not be widened to allow patents that claim different drug substances than the NDA approved drug substance to be listed.
2. Product-by-process patents should not be listed in the Orange Book, or, alternatively, should be restricted to only those patents that claim a new product or new active ingredient.
3. The Regulations should be amended to include timing restrictions on patents eligible for listing. Only patents that were issued at the time a NDA was approved should be listed, unless no patents were issued at the time of NDA approval, in which case the first issued patent would be listed.
4. The FDA should clarify the effect of its proposed changes to other aspects of the Act, for example, the interrelationship between its proposed change to certification process and the application of §505(j)(5)(B)(iii).
5. FDA should also clarify rules pertaining to §505(j)(5)(B)(iii) to ensure that exclusivities relating to newly listed patents do not block generic applicants that have already filed ANDAs at the time the newly listed patent appears in the Orange Book and also to allow generic applicants that are not sued upon delivering a paragraph IV certification but are still delayed due to a first filer's paragraph IV certification, to trigger the first filer's exclusivity.

I LISTING CRITERIA

1. The Proposed Rules significantly and improperly expand the types of patents eligible for listing in the Orange Book

In its Proposed Rules, FDA proposes to expand the type of patents eligible for listing in the Orange Book by including patents that claim non-approved drug substances and certain product-by-process patents. Apotex strongly objects to this initiative.

Patent listings in the Orange Book are of particular concern in that they allow the triggering of 30-month stays of approval. If successive 30-month stays are precluded, as suggested by the Proposed Rules, yet the scope of patents that a generic applicant must address is widened, the generic applicant would be subjected to greater numbers of lawsuits and greater opportunities for stays. These lawsuits and stays are themselves a significant barrier to generic entry.

FDA acknowledges in the Proposed Rules that it has previously interpreted the regulations as requiring that the patent submitted for listing in the Orange Book must assert a claim to the approved drug substance or the approved drug product³. FDA has recognized that its proposal to amend its regulations to expand the categories of patents eligible for inclusion in the Orange Book represents a significant departure from its previous position:

We recognize that allowing NDA applicants and NDA holders to submit such patent information appears to conflict with our longstanding position that the patent must claim the approved drug product or the drug product that is the subject of the application.⁴

The expansion of listings to include patents that do not claim the approved drug product has a profound impact on the listing of drug substances, since there are virtually limitless numbers of variations on what is essentially the same chemical moiety.

Since the Hatch-Waxman amendments were introduced in 1984 there has been a dramatic expansion in the number and type of patents covering significant drugs. This has been accompanied by an equally dramatic expansion of new listings and 30-month stays. The opportunity for new patents and new patent listings to delay generic entry is dramatically illustrated in the following excerpt from a presentation of Eric Larson of Pfizer Inc.⁵

³ Applications for FDA Approval to Market a New Drug: Patent Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not be Infringed, 67 Fed. Reg. 65448 (October 24, 2002) (to be codified at 21 CFR Part 314). ("Proposed Rules") at 65449.

⁴ Proposed Rules at 65452.

⁵ Eric R. Larson, Pfizer, Inc., "Evolution of IPR and Pharmaceutical Discovery and Development" presented at Conference on Intellectual Property Rights: How Far Should They be Extended? (April 27, 1998) available at <http://www7.nationalacademies.org/step/Larson_ppt.ppt> This

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- *“The nature of patent protection around pharmaceutical products changed markedly over the past decade.*
- *Patent coverage around earlier products, such as Norvasc was fairly limited in scope, maybe half-a-dozen or so key patents.*
- *Now, products entering the market may be covered by 25 or more issued patents an pending applications.*
- *While the core patents still afford tremendous protection, newer claims can afford substantial market positions, or at a minimum, slow generic entry by a matter of years. Prozac will enjoy three-years of additional market exclusivity beyond its parent composition of matter patent because on PDE5 inhibitors for the treatment of sexual function may play a key role in protecting sildenafil from both innovator and generic competitors.*
- *Our innovation in drug discovery and development has opened up valuable opportunities for enhancing commercial value of our products.*
- *And this trend isn't going to go away.”*

[Emphasis added]

presentation was obtained from a public source on the Internet and is reproduced in its original form, including Mr. Larson's speaker's notes.

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Pharmaceutical Patents - The Changing Landscape

Intellectual
Property
Strategic
Planning

1980's

- Primary uses
- Processes and Intermediates
- Bulk forms
- Simple formulations
- Composition of matter

1990's

- Expansive numbers of uses
- Methods of treatment
- Mechanism of action
- Packaging
- Delivery profiles
- Dosing regimen
- Dosing range
- Dosing route
- Combinations
- Screening Methods
- Chemistry Methods
- Biological Target
- Field of use
- Primary uses
- Processes and Intermediates
- Bulk forms
- Simple formulations
- Composition of matter

STEPB020399



Innovation will continue, IP sources increase

Intellectual
Property
Strategic
Planning

Claims for each NCE -

- Business Models
- Enabling software
- Patient Markers
- Expansive numbers of uses
- Methods of treatment
- Mechanism of action
- Field of use
- Delivery profiles
- Dosing regimen
- Dosing range
- Dosing route
- Combinations
- Packaging
- Screening methods
- Chemistry Methods
- Biological Target
- Primary uses
- Processes and Intermediates
- Bulk form
- Simple formulations
- Composition of matter

Potential Inventors

Portfolio Decision and Analysis, Finance, Marketing
IT, Biometrics
Genomics, Clinical Diagnostics and Measurements
Clinical, Discovery Biology, Drug Safety, Marketing
Clinical, Discovery Biology
Disc. Biology, Molecular Biology
Disc. Biology, Molecular Biology
Clinical, Drug Metabolism, Pharm R&D
Clinical, Discovery Biology, Gen. Pharm, Marketing
Pharm R&D, Marketing
Discovery Biology, Drug Safety, Drug Metabolism
Discovery Chemistry, Process R&D
Genomics, Discovery Biology
Discovery Biology, Clinical
Discovery Chemistry, Process R&D
Discovery Chemistry, Process R&D, Pharm R&D
Discovery Chemistry, Pharm R&D
Discovery Chemistry, Process R&D

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Apotex is not alone in commenting on the abuses of Orange Book patent listings, although the above presentation by a Pfizer executive is just one blatant example. It is notorious that many later issued patents cover only minor modifications to the already approved product. As President Bush has recognized:

When a drug patent is about to expire, one method some companies use is to file a brand new patent based on a minor feature, such as the color of the pill bottle or a specific combination of ingredients unrelated to the drug's effectiveness. In this way, the brand name company buys time through repeated delays, called automatic stays, that freeze the status quo as the legal complexities are sorted out.⁶

In view of the articulated policies of the statute, Apotex urges that FDA resist any move to expand the type of patents eligible for listing in the Orange Book.

2. Unwarranted effects of expanded listing – 180-day exclusivity

The Proposed Rules would limit the number of stays a generic would be subjected to as a result of new listings. However, listings have another substantial effect in the ability to market a generic product, namely the availability of 180-day exclusivity. While FDA has suggested that its Proposed Rules do not affect the eligibility for 180-day generic exclusivity⁷, if FDA expands the number of patents eligible for listing in the Orange Book, it will expand the opportunity for different applicants to obtain 180-day exclusivity.

While the agency seeks to combat the issue of multiple 30-month stays of approval generic applicants, generics may still be precluded from entering the market by virtue of §505(j)(5)(B)(iv) [21 U.S.C. §355(j)(5)(B)(iv)]. This provision provides that, in effect, a generic applicant that submits a paragraph IV certification will not be eligible for approval if a prior applicant has already submitted a paragraph IV certification. The agency has most recently interpreted this section as allowing multiple exclusivities relating to separate patents offering the same product.⁸

In practical terms this means that a generic applicant that is otherwise approvable may be precluded from receiving final approval due to the eligibility of another generic applicant from receiving 180-day exclusivity. For example, in the event that a patent is listed in the Orange Book on the eve of generic approval, there is the

⁶ Remarks by President George W. Bush on Prescription Drugs, Office of the Press Secretary, October 21, 2002.

⁷ Proposed Rules at 65457.

⁸ See letter to Andrx Pharmaceuticals Inc. from G. Buehler, November 16, 2001, found at <www.fda.gov/cder/ogd/shared_exclusivity.htm> ("Shared Exclusivity Letter").

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potential for the first-filer on the last-listed patent to obtain a blocking right preventing other generic applicants (that have already submitted ANDAs and have already certified to any other relevant patent) from obtaining approval.⁹

Apotex believes that the availability of 180-day exclusivities, and the resulting confusion that can arise from blocking exclusivity scenarios, is another policy ground for the agency to decline to expand the types of patents eligible for listing in the Orange Book.

This and other problems with the application of §505(j) are addressed more fully below in section IV.

3. Statutory criteria - content restrictions

Drug patents that qualify for listing in FDA's Orange Book are unambiguously defined in §505(b)(1) and (c)(2). FDA has stated in the Proposed Rules the standard for listing in the Orange Book – that is, the two prong test:

Thus, both the act and our regulations establish two distinct criteria for a patent intended for listing in the Orange Book: (1) The patent must claim the approved drug product or a method of using the approved drug product; *and* (2) the patent must be one with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the patent owner sought to engage in the drug's manufacture, use, or sale (emphasis added).¹⁰

The word “claim,” as used in Hatch-Waxman, has been held to have the same meaning that it does in patent law, *i.e.*, “that portion of the specification that defines the patent owner's property rights in the invention.”¹¹

The analysis for determining the legality of an Orange Book listing is identical to the analysis used in any patent infringement case, except once the claims of the relevant patent are properly construed, they are applied to the product that is the subject of the approved NDA rather than to an alleged infringer's product. We now turn to that analysis in order to demonstrate that the Proposed Rules' expansion of the types of patents eligible for Orange Book listing is legally unsupportable.

⁹ In *Purepac Pharmaceutical Co. v. Thompson, et al.* D.D.C. Civil Action No. 02-1657 (ESH), appeal pending, Purepac successfully argued that it need not certify to a particular patent. Purepac also argued that its exclusivity on the last issued patent prevents other generic applicants from being approved; the Court has left this issue to the agency to determine.

¹⁰ Proposed Rules at 65449.

¹¹ *Hoechst-Roussel Pharm., Inc. v. Lehman*, 109 F.3d 756, 758, 761, 42 U.S.P.Q.2d 1220, 1222, 1224 (Fed. Cir. 1997).

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Apotex agrees with the text of the Proposed Rule which provides that the patent must claim the drug that is the subject of an approved or pending application, “the applicant shall submit information only on those patents that claim the drug substance that is the subject of the pending or approved application.” Apotex parts ways with FDA over *how* to define which types of patents qualify as the subject of an approved or pending application.

As FTC stated in its citizen petition,¹² that to qualify for listing the patent must claim the approved drug. The *Pfizer* decision¹³ makes clear that the patent must claim the drug product in all respects. The rationale of this interpretation is that a generic seeks to compare its product to the approved product and avoid submission of original clinical trials. The intent of Congress was that if a generic applicant intended to obtain the advantage gained by reliance on innovator data, they should be subject to the certification, preapproval litigation and stay features of the Act. However, this logic does not apply where the patentee has not sought approval for the product or method of use which is claimed by the patent.

Congress intended to achieve a balance between ensuring availability of low cost alternatives, and promoting innovation by including in the Orange Book the original patents on the active pharmaceutical ingredient, the formulation and the methods of use available at the time the NDA was approved (§505(b)(1)), and also by imposing a content requirement – approved drug substance, product and method of use (§505(b)(1)).

In the Proposed Rule, the agency cites the evolution of its policy respecting which patents are eligible for listing. It notes the change in the regulations from “drug product” to “drug substance”. However nowhere does it distinguish the *Pfizer* case, but instead seeks to reconcile the *Pfizer* case to broaden the number of patents eligible for listing. Importantly, the *Pfizer* case recognized that it is a specific drug product (and now drug substance) which is eligible for listing. It is a question of claim construction: does the patent submitted for listing claim the specific drug substance or drug product approved by the agency?

Accordingly, Apotex supports the explicit exclusion of process patents, patents claiming packaging, patents claiming metabolites and patents claiming intermediates. However, Apotex also submits that the following types of patents should also be excluded from the scope of patents eligible for Orange Book listing:

- (i) Different forms of drug substances; and

¹² Bureau of Competition and Policy Planning Staff of the Federal Trade Commission, Citizen Petition to the Commissioner of Food and Drugs pursuant to 21 C.F.R. §§ 10.25(a) and 10.30 - May 16, 2001.

¹³ *Pfizer v. FDA*, 753 F. Supp. 171 (D.Md. 1990).

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(ii) Product-by-process patents.

i) Different forms of drug substances should not be listed

FDA has proposed to include unapproved forms of a drug substance on the basis that it treats these forms as the “same” for the purpose of determining eligibility for an ANDA. But FDA has appeared to confuse the pharmaceutical equivalence requirement for the purposes of generic approval, with the Orange Book listing requirements. Apotex submits that FDA has no discretion under the Act to list patents on different forms of the drug (e.g. so-called polymorph patents), because such patents do not claim the drug, as required by the Act. As such, FDA’s Proposed Rule conflicts with the plain language of the Act and would be invalid. FDA’s policy on equivalence is derived from an entirely different portion of the Act, is therefore irrelevant to this issue, and does not in any way support the Proposed Rule.

The agency has justified its new approach by pointing out that FDA treats different polymorphic forms of an approved substance as the “same” for the purpose of determining bioequivalence:

However, if that patent owner also had a patent on the anhydrous form and the NDA holder were not allowed to submit patent information on the anhydrate because the patent does not claim the approved drug product, the ANDA applicant consulting the Orange Book would have no notice of the patent claiming the anhydrate. The missing patent information could mislead potential ANDA applicants into submitting ANDAs containing the anhydrate and unknowingly infringing the patent claiming the anhydrate.¹⁴

There are at least two critical errors in FDA’s proposed approach:

1. FDA proceeds on the mistaken premise that but for the listing of the patent in the Orange Book, generic applicants would be unaware of a patent on a different polymorphic form of a drug and mistakenly develop and market an infringing product; and
2. FDA ignores a plain reading of the statute that specifically differentiates between listing criteria and eligibility for generic approval.

First, with respect to FDA’s concern about the so-called notice function of the Orange Book, while the listing of patents at one time may have assisted generic applicants, that time has long since passed. When the Act was introduced in 1984 the generic industry was in its infancy. At that time, generic applicants may have

¹⁴ Proposed Rules 65453.

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found it difficult to conduct necessary searches to determine what patents applied to specific products. NDA holders were not forthcoming with this information and it was only later that the Orange Book provided a convenient way for applicants to determine which patents posed a potential barrier to entry.

Today, generic companies are substantial entities that conduct patent searches before applying for a product, and continue to monitor patent applications during the period an NDA is being reviewed by the agency. It should also be noted that the Orange Book has never served as a complete listing of all relevant patents that may pose infringement problems. Process patents pose a barrier to entry but these are excluded from listing in the Orange Book.

Second, the Act (§§505(b)(1) and (c)(2)) specifically defines what type of patents are eligible for listing and this standard requires the subject patent to claim the approved drug (see discussion of the term “claim” above). The eligibility for generic approval is found in a different section of the Act - §505(j)(2)(A)(ii)(I).

This section of the Act requires that an ANDA contain “information to show that the active ingredient in the new drug is the same as that of the listed drug.” §505(j)(2)(A)(ii)(I). FDA has the discretion to determine that a difference in the chemical structure of the active ingredient approved in the innovator company’s NDA and the active ingredient in the ANDA are “the same drug” for the purpose of subsection (j), if the difference in chemical structure has no clinical significance for use by patients.¹⁵

FDA’s reply to Apotex’s citizen petition confirms that FDA exercised this discretion in this instance:

Please note that *for purposes of the same active ingredient requirement in 505(j)* [21 U.S.C. 355(j)], FDA considers anhydrous and hemihydrated forms of drug substances to be pharmaceutical equivalents and to contain the same active ingredient (Orange Book (20th Ed. 2000)).¹⁶

FDA has not adopted, and cannot reasonably adopt, the same position with respect to the entirely separate patent listing requirements of §505(b)(1) and (c)(2). Instead, FDA’s regulation on what patents may be submitted for listing tracks the clear language of the Act. See 21 C.F.R. §314.53(b) (“An [NDA] applicant ... shall submit information on each patent that claims the drug or a method of using the drug that is the subject of the new drug application. . . .”) Thus, while a difference in chemical structure may be immaterial for determining ANDA eligibility, it is significant for

¹⁵ *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998).

¹⁶ Ex.L, FDA Response to Apotex’s Citizen Petition at 6, fn. 16.

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preventing delays in ANDA approval as a result as a result of improper patent listings.

As FTC has noted:

“The FDA typically grants approval through an NDA to a brand-name company to sell only one polymorph of an active ingredient. The company may not sell other versions of the active ingredient without FDA approval...different polymorphs of the approved active ingredient are not part of the approved drug product, and patents claiming the different polymorphs do not claim the approved drug product, thus making the listing of such patents questionable.”¹⁷

Apotex supports this construction of the statute. FDA has no legal authority to allow different forms of the same drug substance to be eligible for Orange Book listing.

ii) Product-by-process patents that claim old products are not eligible for listing in the Orange Book

FDA has also proposed to include certain product-by-process patents “because they are a type of product patent”. In issuing its Proposed Rule, FDA has also sought guidance as to how to determine whether only appropriate product-by-process patents are listed. Apotex submits that no product-by-process patents be listed as they are really process patents in disguise.

Although it is true that product-by-process patents do contain claims which are in product form,¹⁸ such claims are restricted to the process used to make the product. In almost every case, these product claims are not themselves inventive and do not cover any new active drug ingredient. The invention for which the patent is issued is actually the process. So, as a matter of form, the patent contains claims to a product, but as a matter of substance, the invention (and thus the right to obtain a patent) is that the process for making the drug substance is new.

Product-by-process claims were intended for the situation where there is no other way of describing a product except by how it is made. In the pharmaceutical industry, there are very few (if any) active molecules that cannot be described in product terms (by chemical structure or physical properties). However, many product-by-process patents have issued that claim an already-patented active ingredient.

¹⁷ Generic Drug Entry Prior to Patent Expiration: An FTC Study, Federal Trade Commission – July 2002, page A-41

¹⁸ Typical product-by-process claims are in the format “The compound X when made by the process of claim 1”.

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The following examples illustrate the difference between product claims and product-by-process claims:

Product claim:

1. Crystalline paroxetine hydrochloride hemihydrate (U.S. Patent No. 4, 721,723)

Process claim:

8. A process for preparing paroxetine comprising obtaining a compound of structure (1) in which X is 4-fluoro by a process as claimed in claim 7, replacing the 3-hydroxymethyl group by a 3-(3,4-methylenedioxyphenoxy)methyl group, and replacing the substituent R with a hydrogen atom. (U.S. patent No. 6,172,233) [emphasis added]

Product-by-process claims:

11. Paroxetine when prepared according to the process of claim 8. (U.S. patent No. 6,172,233) [emphasis added]
13. Paroxetine hydrochloride hemihydrate when prepared according to the process of claim 10.

In this example, the product-by-process claim (claim 13) of the '233 patent does not claim a new product but claims a new process to manufacture the known substance, paroxetine hydrochloride hemihydrate, which is claimed in claim 1 of the '723 patent.

Listing of product-by-process patents that claim an already-patented active ingredient allows brand-name companies to obtain multiple 30-month stays. The drafters of Hatch-Waxman specifically limited the rewards for innovation to those who developed a new product or a new way of using the product. This is because it is always possible to develop a new way of making old products. Congress did not intend to provide the protection of a 30-month stay for old products. Accordingly, FDA should not allow form to triumph over substance by allowing listing of patent-by-process patents that claim an old product when made by a new process.

Apotex would prefer that no product-by-process patents be eligible for Orange Book listing. But if FDA persists in this approach, at a bare minimum the agency listings should be restricted to only those that claim a new product to avoid further abuses of patent listings.

In order to make sure that only product-by-process claims that cover a new product are listed, Apotex proposes that the NDA holder identify in the declaration:

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1. The product-by-process claims of the patent;
2. The effective filing date of the application for patent;
3. Identify whether the product has been previously sold; and
4. If so, was the product was previously sold more than one year before the effective filing date of the patent application.

If the product (the active ingredient) has been previously sold for more than one year before the effective filing date, it is not eligible for listing as it violates the on-sale bar of 35 U.S.C. § 102(b).

II ONE 30-MONTH STAY PROVISION

1. Description of Proposed Rules

FDA has proposed to eliminate multiple 30-month stays of approval through a changed interpretation of the Hatch-Waxman Act. Specifically, FDA proposes to eliminate the requirement to notify the NDA holder when an ANDA applicant files second or subsequent paragraph IV certifications.

21 C.F.R. §314.95(a)(3) and §314.52(a)(3) would be amended to state that the requirement to provide a notice of invalidity on non-infringement of a patent:

...does not apply to a use patent that claims no uses for which the applicant is seeking approval. This paragraph also does not apply if the applicant amends its application to add a certification under [§314.94(a)(12)(i)(A)(4) for an ANDA applicants or §314.50(i)(1)(i)(A)(4) for 505(b)(2) application applicants] when the application already contained a certification under [§314.94(a)(12)(i)(A)(4) or §314.50(i)(1)(i)(A)(4) to another patent.

An ANDA that contained a paragraph IV certification could not be amended to “include” a paragraph IV certification because it already contained a paragraph IV certification. Thus, the notice requirement of §505(j)(2)(B)(ii) is not triggered. FDA explained the impact as follows:

“Consequently, under section 505(j)(5)(B)(iii) of the act, only one 30-month stay is possible because the subsequent paragraph IV certifications will not have resulted in a second notice to the patent owner and NDA holder, and the 45-day period for filing a patent infringement suit, as described in section 505(j)(5)(B)(iii) of the act, will not have run. To put it another way, if the ANDA applicant is not obliged to submit the notice to the patent owner and NDA holder, then the pre-requisites to trigger the 30-month stay of an ANDA’s approval date are not met, so the 30-month stay would not be available.”¹⁹

Apotex welcomes the intent of this proposal, as it seeks to achieve the policy goal that requires generic applicants to file and provide notice of paragraph IV certifications to eligible patents in Orange Book at the time each applicant files an ANDA. New patents appearing in the Orange Book after a generic applicant submits an ANDA would not delay the ANDA applicant from entering the market due to the 30-month stay.

It is clear that Congress never intended that there be multiple 30-month stays. Apotex believes that the plain language of Hatch-Waxman only permits a single 30-

¹⁹ Proposed Rules at 65455.

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month stay per ANDA. This issue is currently pending before the Federal Circuit in *Apotex v. Thompson*.²⁰ Assuming for the purposes of discussion that FDA is correct that the Hatch-Waxman statutory language is capable of more than one reasonable interpretation, Apotex supports the comments in the preamble to the Proposed Rules that one 30-month stay is consistent with the legislative history of the Hatch-Waxman amendments:

Additionally, we note that interpreting the act to allow only a maximum of one 30-month stay per ANDA or 505(b)(2) application is consistent with the specific legislative history that accompanied the passage of the Hatch-Waxman amendments.²¹

The Hatch-Waxman amendments sought to encourage generics to litigate patents and obtain decisions of invalidity or noninfringement and reward successful applicants. On the brand side, the goal was to prevent erosion of market share where a generic ultimately turns out to be unsuccessful. In appropriate cases, a bond is always available to protect the brand company.

2. Questions and required clarification arising as a result of Proposed Rule

a) If there are no patents in the Orange Book at the time a generic files an ANDA, is the generic applicant required to serve a paragraph IV certification to a patent listed thereafter?

The Proposed Rules address the problem of successive 30-month stays arising after the submission of a first paragraph (IV) certification, but in many cases there are no patents listed in the Orange Book at the time of filing an ANDA that require the delivery of a paragraph IV certification. The Proposed Rules tie the triggering of the 30-month stay to the delivery of a notice to the NDA holder. If the rules are interpreted to require a generic applicant to deliver a paragraph IV certification where no such certification was required at the time of filing of an ANDA, it will lead to a substantial delay in generic approval. Patentees could delay listings until after generic companies apply for approval and thereby gain the benefit of the 30-month stay provision. In addition, a generic applicant that is first to file to the newly listed patent could be a different generic applicant than the one who was first to file a complete ANDA (where there were no listed patents). If all applicants are required to certify to the newly listed patent, the first to file a complete ANDA would be subject to being delayed approval until the expiry of the 180 day exclusivity period afforded the first filer to the newly listed patent. Alternative approaches to this problem are addressed more fully below.

²⁰ *Apotex Inc. v. Tommy G. Thompson, et al.*, U.S. District Court of the District of Columbia, Civ. No. 1:00CV00729.

²¹ Proposed Rules at 65456.

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b) Can the ANDA applicant deliver a second notice?

There are circumstances where an ANDA applicant may choose to voluntarily deliver a certification to a patent listed in the Orange Book after an ANDA is filed. If a patent issues after an ANDA is filed and is listed in the Orange Book, in circumstances where an ANDA applicant has previously filed a paragraph IV certification and previously provided notice to the patentee/NDA holder, under FDA's approach, the ANDA applicant is to deliver a paragraph IV certification to FDA. However, the Proposed Rules do not address whether the ANDA applicant is entitled to deliver voluntary notification of the paragraph IV certification. There are some instances where a generic company would be interested in providing notice of its certification to the brand, in order to obtain a preapproval determination of infringement or invalidity.

Under the Act, the brand has the entitlement to commence a claim on receipt of a notice. There is an incentive to commence the claim under Hatch-Waxman when the brand is entitled to a 30-month stay of approval. A brand may choose not to sue and wait until the generic applicant enters the market and seek injunctive relief. If a court grants a preliminary injunction, the generic would be delayed even further, that is, the period of time it takes to resolve the litigation, effectively creating a further period of time free from generic competition.

c) If the ANDA applicant does deliver a second notice, can it trigger a second 30-month stay?

One reading of the Proposed Rules says that a 30-month stay would be triggered by delivery of a voluntary second notice. The Proposed Rules state:

Consequently, under section 505(j)(5)(B)(iii) of the act, only one 30-month stay in the ANDA's approval date is possible, because the subsequent paragraph IV certifications will not have resulted in a second notice to the patent owner and NDA holder, and the 45-day period for filing a patent infringement suit, as described in section 505(j)(5)(B)(iii) of the act, will not have run.

If generic applicant delivers a certification to a NDA holder (where the generic applicant has previously delivered a certification to the NDA holder), the logic of the proposed regulatory change might suggest a further 30-month stay is possible. From the generic applicant's perspective, it has no interest in triggering a stay but does seek to resolve patent issues prior to market launch. However, the intent of the Proposed Rules appears to be clear: eliminate successive 30-month stays. Accordingly, the Proposed Rules should contain a provision allowing the delivery of additional certifications without triggering further stays.

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- d) If the patentee does not sue, is there any ability on the ANDA applicant to obtain a declaratory judgment of non-infringement or invalidity as there may be no reasonable apprehension of suit?**

Under the current scheme, even where a generic applicant provides notice of a certification to a NDA holder, the NDA holder does not necessarily commence a lawsuit against the generic applicant. If the generic applicant is concerned about possible infringement and does not want to enter the market at risk, it may be entitled to seek declaratory judgment relief where they have a reasonable apprehension of suit. Although the rights of patentees to sue for patent infringement are clearly unaffected by FDA's proposed approach, it is unclear whether there is an impact on the ability of a generic to obtain preapproval litigation due to the standard of a reasonable apprehension of suit/case in controversy.²² If the brand is only notified of the first paragraph IV certification, it may not sue on the subsequent patents. A generic's decision not to provide notice of a paragraph IV certification could negatively impact its ability to say that it has a reasonable apprehension of suit.

- e) If an ANDA applicant is not required to deliver a paragraph IV certification to the NDA holder, is the first-to-file a paragraph IV certification to the relevant patent entitled to any form of exclusivity?**

The Proposed Rules cast some doubt over whether a first filer to a newly listed patent should enjoy any form of exclusivity. As we set out below, the purpose of the exclusivity provision was to encourage generic applicants to seek approval for a generic version of an approved drug prior to patent expiry. This purpose is achieved where the generic applicant submits a complete ANDA and challenges a listed patent. If the generic applicant does not challenge the listed patent, by delivering a paragraph IV certification to the NDA holder, there is some doubt whether the generic applicant should be entitled to any form of exclusivity that could act to block other generic applicants. The proposed rules should clarify that enjoyment of exclusivity is contingent upon serving a paragraph IV certification not only on FDA but also on the patentee and NDA holder.

- f) If the patentee does not sue, what constitutes a court decision sufficient to trigger a first filer's exclusivity under §505(j)(5)(B)(iii)?**

In the alternative, if a generic applicant is entitled to exclusivity based upon delivery of a paragraph IV certification to FDA but not the patentee and NDA holder, there is some doubt as to what would constitute a court decision sufficient to trigger 180-day

²² See *Vanguard Research, Inc. v. Peat, Inc.*, 304 F.3d 1249 (Fed. Cir. 2002); *Cordis Corp. v. Medtronic, Inc.*, 835 F.2d 859, 862 (Fed. Cir. 1987); *Jervis B. Webb Co. v. Southern Sys., Inc.*, 742 F.2d 1388, 1398-99 (Fed. Cir. 1984).

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exclusivity. Section 505(j)(5)(B)(iii) states that exclusivity can be triggered by a court decision or first commercial marketing.

In the case where there are two patents listed at different times in the Orange Book, there is no obligation on the generic applicants certifying to the second patent to give notice of a paragraph IV certification to the NDA holder. In that event, there may be no lawsuit by the brand, yet there may be an exclusivity afforded to the first filer on the second patent pursuant to §505(j)(5)(B)(iii). The first filer to the second patent may choose not to enter the market at risk and instead obtain a declaratory judgment of invalidity or non-infringement. Another applicant may choose to enter the market at risk, but would have to wait until the first filer's exclusivity relating to the second patent has run. Given that there are only two triggering events in the statute causing a first filer's exclusivity to run, namely a court decision or commercial marketing, the agency should clarify whether and how an exclusivity may be triggered in the above situation. The interrelationship between patent listing and § 505(j)(5)(B)(iv) is described more fully below in section IV.

In answering all of the above areas of clarification, Apotex believes that the following are the objectives of the regulatory regime as they relate to the approval of generic products:

1. A predictable interpretation of the legislation;
2. An interpretation that is easier to apply;
3. An interpretation that results in fewer lawsuits over interpretation; and
4. An interpretation that encourages generic entry and rewards the innovation of generic companies in either attacking or designing around existing patent protection resulting in the availability of a low cost generic product prior to patent expiry.

It is important for the agency to follow these principles in further clarifying the 30-month stay provision in the manner discussed above.

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1. One 30-month stay based on section 505(j)(5)(B)(iii)

In view of the uncertainty in the application of FDA's proposed rule, Apotex offers the following alternative approaches to address the listing and stay problems identified by the agency and the FTC.

FDA acknowledged considering one approach that was offered by the Generic Pharmaceutical Association (section 505(j)(5)(B)(iii) of the Act refers to "the" 30-month stay).²³ The agency stated in its Proposed Rule that this alternative approach could lead to abuse as a generic applicant could file a paragraph III certification then switch it later to a paragraph IV certification to avoid the automatic stay. This possibility could, of course, be addressed by the agency in regulations. The regulations already contain a provision respecting amended certifications (21 C.F.R. 314.94(a)(12)(viii)). The section provides that once an amendment or letter is submitted, the application will no longer be considered to contain the prior certification. Arguably, in the example cited above, a new paragraph IV certification would replace the earlier filed paragraph IV certification and the generic applicant would be subject to a 30-month stay. However, the agency should enact a new regulation that specifically addresses this concern.

Arguably, the interpretation of the Act allowing one 30-month stay that is based on the reading of section 505(j)(5)(B)(iii) above is preferable to the Proposed Rules in that it would be clear that a generic applicant could give notice of new paragraph IV certifications to newly listed patents (and obtain pre-approval determination of patent issues) without invoking successive 30 month stays.

2. Timing approaches to limiting 30-month stays may be preferable to those advanced by the agency

Apotex believes that the plain language of Hatch-Waxman limits the eligibility of patents for listing based on when the patent is obtained. Based on a plain reading of §505(b)(1) and (c)(2) there is not only a content requirement but a timing component as well. The critical date for assessment of a patent's eligibility is the date of approval of the NDA. Apotex believes that this timing restriction may be the decisive one in limiting successive 30-month stays.

Patent information may be filed with the NDA, and this information can be amended to add patents prior to approval of the NDA (§505(b)(1)).²⁴ FDA is to publish this

²³ Proposed Rules at 65455.

²⁴ §505(b)(1)(F) Specimens of the labeling proposed to be used for such drug. The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application of which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such a

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information upon approval of the application. Subsection(b)(1) sets out the general rule: patents are eligible for listing if they are included with the patent information filed with the NDA, (“shall file with the application the patent number... of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug”).

If patents issue during the review period, they are to be included before approval of the NDA. (“If an application is filed under this subsection for a drug and a patent which claims such a drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence”).

The only modification to that eligibility requirement of §505(b)(1) is in (c)(2)²⁵ which contains a narrow exception. Where no patent information has been submitted before approval of the NDA, newly issued patents can be added after the date of the NDA, as long as they are submitted within 30 days. (“if the holder of an approved application could not file patent information under subsection (b) of this section because no patent had been issued when an application was filed or approved, the holder shall file such information under this subsection not later than thirty days after

drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A).

²⁵ §505 (c)(2) If the patent information described in subsection (b) of this section could not be filed with the submission of an application under subsection (b) of this section because the application was filed before the patent information was required under subsection (b) of this section or a patent was issued after the application was approved under such subsection, the holder of an approved application shall file with the Secretary the patent number and the expiration date of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If the holder of an approved application could not file patent information under subsection (b) of this section because it was not required at the time the application was approved, the holder shall file such information under this subsection not later than thirty days after September 24, 1984, and if the holder of an approved application could not file patent information under subsection (b) of this section because no patent had been issued when an application was filed or approved, the holder shall file such information under this subsection not later than thirty days after the date the patent involved is issued. Upon the submission of patent information under this subsection, the Secretary shall publish it.

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the date the patent involved is issued”). In other words, if patent information had already been submitted, the NDA holder could not submit further patent information. The NDA holder either submits patent information before the NDA is approved, or after the NDA is approved, not at both times, and not throughout the entire life of the drug.

The effect of this approach is to permit only one 30-month stay, as even if multiple patents are listed initially, they are all addressed at the same time, and the stays for each patent run concurrently. FDA has acknowledged in briefs filed in various courts that the statute does not address whether patents issued after an NDA has been approved are eligible for listing:

On November 21, 2000, FDA denied the requests in the petition [Lord Bissell & Brook petition rejecting patent listings affecting Paxil] and provided the following analysis. A.R., tab 8. FDA explained that it was following the procedures set forth in the applicable regulation that provided for the listing of the patents. In promulgating these regulations, FDA permissibly interpreted the controlling statutory provisions of the FDCA, 21 U.S.C. § 355 (b) (1) and (c) (2). The statutory language does not make clear whether a newly issued patent may be listed after an NDA is approved 1) only when no patent was available at the time the NDA was filed, or 2) when the information on that specific patent was not available at the time the NDA was filed. FDA, through notice and comment rule-making, properly adopted the latter interpretation: the NDA applicant may submit information on newly issued patent within 30 days of the date the patent was issued, without regard to whether another patent was listed at the time the NDA was filed. 21 C.F.R. § 314.53 (d) (3). FDA followed that regulation in the instant case in listing the later submitted patents. [*emphasis added*]²⁶

Patents filed after the NDA is approved cannot claim the approved product due to the fact such patents would not be valid as covering old, known subject matter (and thus anticipated pursuant to 35 U.S.C. §102(b)). These later-issued patents do not represent real innovation, and were never intended by Congress to be listable. Congress showed its intent to limit the types of patents eligible for the extraordinary remedy of the automatic 30-month stay. For example, process patents are not eligible.

²⁶ Memorandum in support of Federal Defendants’ Motion to Dismiss and in opposition to Motion of Preliminary Injunction, *Apotex Inc. v. Tommy G. Thompson, et al.*, U.S. District Court of the District of Columbia, Civ. No. 1:00CV00729 (TPJ) at page 14.

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The merit of this approach is that it restricts the application of 30-month stays. In effect, no ANDA is subject to more than one 30-month stay as the stay operates from the time the notice is given. Even if there are multiple patents, all stays run concurrently. It also restricts the number of applicants entitled to 180-day exclusivity to the first to file an ANDA, as that sponsor will most likely certify to all listed patents. Even if patents are issued after an ANDA is filed, then that ANDA applicant would not need to certify to these patents and the applicant would not be entitled to 180-day exclusivity.

Apotex thus proposes FDA adopt the following approach:

1. Patents issued by the time the NDA is filed are filed with the NDA (§505(b)(1)).
2. Patents issued by the time the NDA is approved result in the NDA holder amending the application prior to approval to include this patent information (§505(b)(1)).
3. After the NDA is approved, if no patent information had been previously submitted under (b), the information is filed within 30 days after issuance of the patent (§505(c)(2)).
4. After the NDA is approved, patents cannot be added to the Orange Book unless no patent was available at the time the NDA was approved.

While this approach may represent a slight departure from the recent practice of FDA allowing multiple exclusivities including an exclusivity based on the most recently issued patent, even after an ANDA has been filed, it addresses the problems created by multiple periods of exclusivity and the potential effect that all applicants would be delayed final approval pending resolution of the patent issues on the last issued patent.

g) No requirements in statute to make multiple certifications

Another suggested approach to preventing abuses of the Orange Book is to not require certifications by ANDA applicants to newly-listed patents, that is, those patents listed after the ANDA was filed. This is the approach adopted by the FTC in their study released in July, 2002 titled: Generic Drug Entry Prior to Patent Expiration: An FTC Study. Specifically, the FTC recommended:

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Permit only one automatic 30-month stay per drug product per ANDA to resolve infringement disputes over patents listed in the Orange Book prior to the filing date of the generic applicant's ANDA.

The FTC justified this recommendation on the basis that, among other things, the period of 30 months approximates the length of time for FDA to review an ANDA submission, and on the basis that most of the later-issued patents in the Orange Book raise questions about whether the FDA's patent listing requirements have been met.

The content requirements for an ANDA as set out in §505(j)(2)(A) require, among other things, that an ANDA applicant make a certification with respect to each patent listed in the Orange Book which claims the drug or its use for which the applicant is seeking approval.²⁷ Notably, there is no mention of certification to patents that are listed in the Orange Book after an ANDA has been filed. Subsection 505 (j)(2)(A) states:

The Secretary *may not require* that an abbreviated application contain information in addition to that required by clauses (i) through (viii) (emphasis added).

On this reading, the Act prohibits FDA's current practice ostensibly requiring certification for each new patent listing made even after the ANDA has been properly filed. On this reading of the statute, the simplest approach would be to eliminate that requirement.

Read in its entirety, this section is consistent with the provisions of §505(c)(2) regarding the submission of information on patents that issue after an NDA has been approved. An ANDA applicant must certify, in the original application, to all patents that are listed in the Orange Book when the application was filed, whether the NDA-holder submitted information on such patents before the NDA was approved. As set out above, the final sentence of the section forbids FDA from requiring "additional information", such as certifications on patents that are listed after the ANDA has been filed.²⁸

²⁷ §505(j)(2)(A)(vii).

²⁸ The plain reading of 21 U.S.C. §355(j)(2)(A) is confirmed by another prominent element of Hatch-Waxman, the "statutory infringement" provision of 35 U.S.C. § 271(e)(2): ("It shall be an act of infringement to *submit – (A) an application* under section 505(j) of the Federal Food, Drug and Cosmetic Act 21 U.S.C. § 355(j)..."). Congress contemplated only one act of statutory patent infringement: the filing of the original ANDA. The idea, necessarily implicit in FDA's

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The statutory interpretation advocated here is consistent with the essential notice function served by Orange Book listings. The listing provision is intended to allow generic companies to make informed decisions about whether time and resources should be invested in the development of a particular product. This intention is obviously subverted by the requirement that ANDA applicants certify to patents listed after the ANDA was filed.

The problems that arise from the unlawful requirement that ANDA applicants certify to late-listed patents are further compounded by FDA's approach whereby it refuses to police patent listings. It is unlikely that Congress intended that there be unlimited, non-scrutinized patent listings, coupled with a requirement that certifications for every patent would follow, triggering multiple 30-month stays.

4. Supplements do not provide an opportunity to list patents

FDA has adopted a regulation that allows innovators who file a supplement to an approved NDA, requesting a change in the composition, formulation, or method of use of an approved drug, to supply information on patents relating to the change.²⁹ If FDA approves the change, the relevant patents are listed in the Orange Book.³⁰

The language of the Act, properly construed, does not authorize the listing of patents that do not claim the innovator's drug as *originally* approved. The relevant section of the statute, §505(c)(2), authorizes the submission of patent information only on patents that claim the drug as approved in *the original NDA*. The section identifies the relevant filing as the *original* NDA, containing all the information on safety, efficacy, components, manufacturing methods and controls and labeling. The section also uses verbs in the past tense that can only refer to the original NDA (i.e. "for which the patent application *was* submitted"). Thus, Act does not authorize the listing of patents that do not claim the innovator's drug as originally approved.

As a result of FDA's policy enabling listing of patents with a supplement, NDA holders can "evergreen" their monopolies by making minor changes to already-approved drug products. These changes result in the listing of additional patents in the Orange Book, which in turn requires ANDA applicants to make further certifications. In the end, patentees are given the opportunity to file infringement actions in relation to these newly (and inappropriately) listed patents, and obtain further 30-month stays of generic approval. This practice of evergreening is the practice that President Bush seeks to stop with the passage of new Regulations.

reading of the statute, that there can be multiple acts of infringement whenever a newly issued patent is listed in the Orange Book after the ANDA has been filed, ignores the plain test of §271(e)(2).

²⁹ 21 C.F.R. § 314.53(d)(2).

³⁰ 21 C.F.R. § 314.53(e).

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It is also important to note that other sections of the Act support the conclusion that only patents that claim the drug approved in the original NDA can be later-listed in the Orange Book. Congress specifically addressed the issue of NDA supplements in related provisions of the Act that were added by the Hatch-Waxman amendments.³¹ These provisions demonstrate that where Congress believed that supplements to NDAs should be considered a significant element of the statutory scheme, it expressly stated so. Accordingly, the absence of any reference to supplements in respect of patents that are eligible for listing in the Orange Book is significant.

It is further submitted that this approach to patent listing is not contrary to Congress' objective of encouraging research by innovator companies, as it is unlikely that research undertaken after an NDA is approved would produce an advantage of the same magnitude as occurs with respect to the initial patent. This approach to patent listing also comports with Congress' understanding of the realities of new drug development, testing and regulatory review, i.e. that innovators typically file applications for patents relating to a new invention before the NDA was approved, and that any such application had to be filed, at the latest, within one year of approval of the NDA and marketing of the new drug.

³¹ Consider specifically 21 U.S.C. §355(j)(5)(D)(iv) (granting an NDA holder a period of market exclusivity during which no ANDA may be approved: “[i]f a supplement to an application... is approved... and the supplement contains reports of new clinical investigations... essential to the approval of the supplement...”); 21 U.S.C. §355(j)(5)(D)(v) (related transition provision for applications and supplements to applicants approved shortly before the passage of the Act); 21 U.S.C. §355(c)(1)(D)(iv) and (v) (similar provisions relating to § 505(b)(2) NDAs).

IV SECTION §505(J)(5)(B)(iii) ISSUES

While the agency has tried to address one of the major obstacles to expediting generic approval, namely, successive 30-month stays, there are two major obstacles that are not addressed in the Proposed Rules that are causing substantial delays in generic approval. These obstacles are based on the agency's current interpretation of §505(j)(5)(B)(iii), the provision which effectively provides the first generic to file an ANDA, 180 days of market exclusivity.

First, due to the phenomenon of new patent listings appearing in the Orange Book after generic applicants have already filed an ANDA, new opportunities for 180-day exclusivity are arising. There is the opportunity for the first to file on a later issued patents to receive 180-day exclusivity and to prevent all other generics (who may have previously filed an ANDA before the time the new patent appears in the Orange Book), from receiving approval until a court decision in respect of the last issued patent or a first commercial marketing takes place by the first to file on the last issued patent.

Second, generic applicants who file an ANDA subsequently and certify to any listed patents may not necessarily be sued by the NDA holder (despite giving notice of a paragraph IV certification to the NDA holder). This means that the subsequent applicants may have no means to trigger the first filer's exclusivity and could potentially wait years to receive their approvals until the first filer's litigation is complete and the first filer has enjoyed 180-day exclusivity.

The agency has the ability to address these problems within the existing statute and without disturbing the existing regulations. Each of these problems and potential solutions are addressed below:

a) Ability of first filer to later issued patent to delay approval

As set out above, a first filer on a later issued patent has the potential to delay all generic applicants from receiving approval.

In the simplest case, this can occur if there is no listed patent, until a patent appears on the eve of generic approval. The first to file on the newly listed patent would have the potential to delay all generic applicants. This would be because the first filer would be entitled to enjoy its period of 180 day exclusivity, this period would not be triggered until a court decision or first commercial marketing.

Assuming all ANDA applicants file paragraph IV certifications, all generic applicants could be delayed for a period of 30 months (if sued) plus the 180-day period of exclusivity enjoyed by the first filer.

In a more complicated example, at the time the first filer submits an ANDA, there may be one patent listed in the Orange Book. This patent is addressed by the first filer with a paragraph IV certification and the first filer is sued and subjected to a 30-

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month stay of approval. Prior to a triggering event, a new patent appears in the Orange Book that must be addressed but another generic applicant is first to file on the newly listed patent. Under one approach, only the first applicant to file an ANDA containing a paragraph IV certification would be entitled to the benefit of 180-day exclusivity (FDA has defined this as “the One First Applicant” approach).

“if the application contains **a certification...**and is for a drug for which a previous application has been submitted under this subsection containing such a certification...” [emphasis added]

This ties the entitlement to exclusivity to the act of filing a certification – it does not require the identification of any particular patent in the certification.

FDA has defined the approach as follows:

"One First Applicant" Approach: FDA would approve only the ANDA of the applicant who filed the first paragraph IV certification for any patent, regardless of the patent for which it was submitted. That applicant's exclusivity would then begin to run with first marketing or a court decision on the patent that is the subject of the first certification. During the exclusivity period the agency would approve no other ANDA for the listed drug. When the exclusivity expired, all subsequent applicants would be eligible for approval if they otherwise met the approval requirements.

Under another approach, both applicants that are first to file to different patents share in the 180-day period of exclusivity (FDA has defined this as “Shared Exclusivity” approach).

The agency defines this approach as follows:

“Shared Exclusivity” Approach: When different applicants have submitted first paragraph IV ANDAs for different listed patents, FDA will approve the ANDAs that are first for any listed patent as soon as they are otherwise eligible for approval. Exclusivity for all the ANDAs will be shared and will be triggered by either first commercial marketing of any first applicant or a court decision on any one of the patents that qualified any applicant for exclusivity. During that “shared” exclusivity period, FDA may approve any ANDA eligible for exclusivity, but no other ANDA. This may result in no applicant having a period when it is the only generic product

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on the market, but it will limit the number of ANDAs approved during the exclusivity period to the number of “first” applicants.³²

One problem occurs where the first applicant’s exclusivity is triggered by a court decision (by another generic applicant’s litigation) but the first applicant is not entitled to final approval because it is subject to a 30 month stay of approval or because it is subject to the exclusivity of the applicant that is first to file on the second patent. Allowing a first filer’s exclusivity to expire, yet precluding approval based on another’s first filer’s exclusivity based on a later patent, has potentially far reaching and detrimental consequences. This is perhaps best explained by noting that there is no reason to assume that further patents will not be listed in the Orange Book leading to further opportunities for exclusivity. Each first filer’s exclusivity could be triggered by another applicant (a court decision) yet a new patent could be issued leading to further exclusivities. This pattern could continue almost indefinitely with the result that a generic product would never enter the market.

Such an approach:

1. Acts as a disincentive for first to file to vigorously pursue litigation and grossly penalizes the ANDA applicant that moves quickly to resolve litigation and obtain the benefit of exclusivity;
2. Rewards the last-in, the first to file on the latest patent, by effectively granting 180-day exclusivity to the last first filer on the latest patent; and
3. Encourages further patent extension strategies by rewarding companies who are successful in obtaining listing of patents shortly before generic entry with not only 30-month stays of approval but also further delays until paragraph IV litigation involving the last listed patent is resolved.

Such an interpretation would lead to a manifestly absurd result³³ and would not be in accordance with Congress’s plain purposes in enacting the statute (“to make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962”).³⁴ Further, the Supreme Court has made it clear that tribunals should avoid circumstances that “seriously impair the effectiveness of the Act” in accomplishing its purpose.³⁵

³² Shared Exclusivity Letter, *supra* note 8.

³³ It is a common mandate of statutory construction to avoid absurd results. See e.g., *Green v. Bock Laundry Machine Co.*, 490 U.S. 504, 510-511 (1989); *Trans Alaska Pipeline Rate Cases*, 436 U.S. 631, 643 (1978); *Commissioner v. Brown*, 380 U.S. 563, 571 (1965); *Helvering v. Hammel*, 311 U.S. 504, 510-511 (1941); *United States v. Katz*, 271 U.S. 354, 357 (1926); *Caminetti v. United States*, 242 U.S. 470, 490 (1917); *United States v. Kirby*, 74 U.S. (7 Wall.) 482, 486-487 (1869).

IV SECTION §505(J)(5)(B)(iii) ISSUES

Arguably, the Act only prevents FDA from approving an ANDA if that application contains a certification (to a patent) where a previous applicant had submitted a certification to the same patent:

§505(j)(5)(B)(iii) “If the application contains a certification described in subclause (IV) of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection containing such a certification, the application shall be made effective not earlier than one hundred and eighty days after

- (I) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or
- (II) the date of a decision of a court in an action described in clause (iii) holding the patent which is the subject of the certification to be invalid or not infringed,

whichever is earlier...” [emphasis added].

When a new patent appears in the Orange Book after ANDA applicants have submitted a substantially complete application and the applicant certifies to the newly listed patent, no “previous application” containing a paragraph IV certification to that patent has been submitted. Therefore, FDA has no basis to withhold approval from an earlier applicant that was first to file on an earlier listed patent provided the applicant is otherwise entitled to approval.

The end result would be that a person who is first to submit a paragraph IV certification to a newly listed patent would have the right to prevent a certain group of ANDA applicants from receiving approval. This group consists of those which submitted applications after the filing of a paragraph IV certification to the newly listed patent. The first filer on the newly listed patent would not be entitled to prevent existing applicants from receiving approval, but can only prevent new

³⁴ Courts have an obligation to effectuate Congress' plain purposes in enacting a statute. See, e.g., *Holloway v. United States*, 526 U.S. 1, 9 (1999) (noting that statutory language should be interpreted in light of congressional policy); *Caron v. United States*, 524 U.S. 308, 315 (1998) (rejecting petitioner's reading of a statute because it "yields results contrary to a likely, and rational, congressional policy"). See *United States v. Heirs of Boisdore*, 49 U.S. (8 How.) 113, 122 (1849) (interpretation should reach statutory "object and policy.").

³⁵ *United States v. Harriss*, 347 U.S. 612, 623 (1954).

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applicants from receiving approval pending the enjoyment of the first filer's 180 day exclusivity on the newly listed patent.

This approach would mean that the first to file an ANDA containing a paragraph IV certification would not be blocked by any subsequent applicant that is first to file on a newly listed patent.

This approach is consistent with the purposes of the Act for the following reasons:

1. It encourages the challenging of patents by not only the first generic;
2. It encourages early entry of generic products;
3. It encourages the first-to-file to be diligent with litigation so that its exclusivity is not triggered by a later competitor's court decision;
4. It recognizes commercial reality in which the first to file usually must address the broadest and hardest to challenge patents, namely the original product and method of use patents. These types of challenges require challenges to validity (as it is impossible not to infringe the basic product patent and be approved by FDA) and take significant resources; and
5. It provides that the value of subsequent rewards of 180 day exclusivity decreases with each subsequent certification.

Should the agency adopt the preceding approach, there still remains the prospect of delays to generic competition when there are no patents listed in the Orange Book when the first to file applicant files its ANDA. If a new patent appears on the eve of generic approval, all applicants could be delayed not only by the 30-month stay but by a new period of exclusivity. In order to avoid this possibility when filing an ANDA, FDA could implement any one of the previous suggestions, namely:

1. Timing approaches to limiting 30-month stays may be preferable to those advanced by the agency;
2. No requirement to certify after submission of a complete ANDA; and
3. Supplements do not provide an opportunity to list patents.

The other solution is to interpret § 505 (j)(2)(A)(vii) (IV) as permitting an applicant to certify that it will not infringe any patent that is currently listed or will be listed in the future in the Orange Book, or that such patent is invalid.

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It should be noted that a paragraph I certification currently allows an ANDA applicant to certify that patent information in respect of the subject drug has not been filed. This may well be accurate at the time that an ANDA applicant delivers a certification. By submitting a paragraph IV certification in the manner suggested above, a generic can signal its intent to challenge all patents later appearing in the Orange Book.

This approach furthers the purpose of the exclusivity provision, i.e. to encourage market entry. This purpose is not furthered when a first to file can be subject to delays due to patent information being listed on the eve of generic approval.

b) Delayed generic approvals based on inability to trigger first filer's exclusivity

Generic applicants that are not first to file a paragraph IV certification to a patent are not allowed to obtain FDA approval until the expiry of the first filer's exclusivity. This exclusivity can be triggered by a subsequent generic applicant by obtaining a court decision. However, in many cases, a subsequent applicant is not sued by the NDA holder. These generic applicants then arguably have no means to trigger the first filer's exclusivity. The decision not to sue a subsequent generic applicant could be a deliberate strategy to ensure no subsequent applicants have the ability to trigger the stay. The brand has an economic incentive to engage in any strategy that delays entry.

Even if a subsequent applicant is not sued, it could attempt to obtain a declaratory judgment of non-infringement or invalidity, thereby triggering the first ANDA applicant's exclusivity. This was done by two generic applicants in *Teva Pharmaceuticals, USA Inc. v. Food and Drug Administration*³⁶, where the U.S. Court of Appeals for the D.C. Circuit held that, under the particular facts presented by that case, FDA should have regarded the dismissal of a declaratory judgment action as the "court decision trigger" for 180-day exclusivity. However, there is some uncertainty in the court's decisions regarding whether any dismissal of a declaratory judgment should be treated by the agency as a court decision within the meaning of §505(j)(5)(B)(iv).

³⁶ *Teva Pharmaceuticals, USA Inc. v. Food and Drug Administration*, 182 F.3d. 1003 involving the drug ticlopidine, TorPharm was first to file a paragraph IV certification to the relevant patent. Teva later filed a paragraph IV certification to the same patent, but was not sued by the patentee. Teva then sued the patentee in order to obtain a "court decision" that would trigger TorPharm's 180-day period of exclusivity. The Court dismissed Teva's complaint for lack of subject matter jurisdiction on the basis of the patentee's admission of non-infringement. FDA refused to accept this decision as a triggering court decision under the Act. Accordingly, Teva sought an injunction requiring FDA to recognize the Court's dismissal of Teva's complaint as a "court decision" under the Act. The United States Court of Appeals for the D.C. Circuit reversed FDA's decision. As a result, TorPharm's exclusivity was triggered and TorPharm did not obtain the full benefit of 180-day exclusivity for ticlopidine.

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FDA should solve this uncertainty by treating similar cases similarly, and adopting a regulation that provides that any dismissal of a declaratory judgment action on the basis of the patentee's admission of non-infringement and resulting lack of a reasonable apprehension of suit by the patent holder, will be regarded as a court decision sufficient to trigger a first filer's exclusivity.

While there is an advantage to subsequent applicants triggering a first filer's exclusivity, there is also a chance that this strategy could be invoked prematurely resulting in the first filer having no opportunity to obtain the benefit of this period of exclusivity. For example, if a subsequent applicant submits an ANDA with a paragraph IV certification shortly after a first applicant, but is not sued, the proposed interpretation (treating the failure of the NDA holder to sue as a court decision), would result in the triggering of the first filer's exclusivity before FDA has reviewed the first filer's ANDA.

In view of this concern, the triggering of the first filer's exclusivity should arguably not occur until the expiry of the 30-month stay period or, the date at which FDA determines that the second filer's ANDA is entitled to tentative approval, whichever is earliest. This period should provide the first filer with sufficient time to obtain a judgment and enter the market.

The overall objective of the Act (to get generic drugs into the market quickly) should be kept in mind. Subsequent applicants are in effect burdened with the first filer's litigation strategy – if a poor argument is made attacking the validity of the patent or the subsequent applicant has successfully designed around a patent (and is eligible for a declaration of non-infringement) – it must wait until the first filer completes its litigation. The purpose of the enactment was to provide an incentive for generics to enter the market quickly, before patent expiry; it was not meant to act as a further barrier to entry.

Apotex trusts that these comments will be of use to the Agency as it completes this vitally important regulatory reform project.