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Memorandum

To Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Date April 30, 2004

Concerning Food and Drug Administration Request for
Comments [Docket No. 2004N-0087]

December 2003 Hatch-Waxman Reforms
(Included as part of Title XI of the Medicare Prescription Drug, Improvement, and Modernization
Act of 2003 (the "Act"))

On behalf of Sandoz Inc. the following comments and requests for guidance with respect to the
effect and intended implementation of the December 2003 Hatch-Waxman Reforms are respectfully
submitted to FDA for its consideration pursuant to FDA's Request for Comments in its March 3,
2004 Federal Register Notice [Docket No. 2004N-0087]:

Thirty (30)-month stay (21 U.S.C. § 355 (j)(5)(B)(iii)): Termination provisions. The language of
the Act is ambiguous as to when the automatic 30-month stay terminates in the event that the NDA
holder brings an action for patent infringement against a generic company with respect to more than
one Orange Book-listed patent. It is important to receive guidance from FDA as to how it intends to
interpret the Act.

Statutory language. The Act provides that if (1) an ANDA Applicant makes a Paragraph IV
certification with respect to one or more patents which claim the listed drug or which claim a use for
such listed drug for which the Applicant is seeking approval, (2) before the expiration of 45 days
after the date on which the NDA holder and the patent owner receive notice thereof, one or both of
them bring an action for infringement of the patent that is the subject of the certification and (3) the
required patent information for such patent was submitted to the FDA for listing in the FDA's
Orange Book before the date on which the ANDA was submitted, then approval of the ANDA will
be made effective upon the expiration of the 30-month period beginning on the date of receipt of the
notice referred to above, except that:

If before the expiration of such 30-month period, the district court decides that the patent is invalid or not infringed, final ANDA approval will be made effective on the date on which the court enters judgment reflecting the decision; or

If before expiration of such 30-month period, the district court decides that the patent has been infringed and the judgment of the district court is appealed, final ANDA approval will be made effective on the date on which the court of appeals decides that the patent is invalid or not infringed (or, if the judgment of the district court is not appealed or is affirmed, on the date of patent expiration).

Purpose of the new provision. As made clear in the Summary of the Medicare Conference Agreement issued by the Committee on Ways and Means, the intent of the changes to the Hatch-Waxman 30-month stay provisions is to assure that “new drug Applicants will receive only one 30 month stay per product for patents submitted prior to the filing of a generic drug application.” According to the Conference Agreement Report, “[t]he single 30-month stay provisions are a centerpiece of [the] legislation, allowing generic products to enter the market more quickly.”

Applicability to multi-patent situations. While it is clear that the objective of the changes is to limit the NDA holder to one 30-month stay per product, the application of the statutory language to multi-patent situations is uncertain. As indicated above, the Act provides that the 30-month stay terminates upon the first decision of a court (district court or court of appeals) that the patent is invalid or not infringed by the generic product. The new provision refers to “the patent” in the singular tense. It does not specifically address the situation in which multiple patents are listed in FDA’s Orange Book.

What happens, therefore, when an ANDA Applicant submits Paragraph IV certifications to more than one patent and the NDA holder brings a patent infringement action with respect to all of those patent challenges? In such an event (which may be commonplace), the language of the Act may be read in one of two ways:

The 30-month stay terminates early upon the first decision of a court that any of the patents as to which a Paragraph IV certification has been submitted is invalid or not infringed by the ANDA product; or

The 30-month stay terminates early if, prior to the expiration thereof, there is a court decision of invalidity or non-infringement with respect to each of the patents as to which a Paragraph IV certification has been submitted.

The first approach would foster the stated objective of assuring that generic products enter the market as quickly as possible. The second approach, however, would assure that the NDA holder is afforded a full opportunity for a 30-month stay per ANDA. Which interpretation will be applied by the agency?

Applicability to multi-ANDA situations. The application of the Act to multiple ANDA situations is also unclear. As indicated above, the Act provides that the 30-month stay terminates early upon a decision of the district court or the court of appeals, as the case may be, that the patent is invalid or not infringed. As in the case of multiple patents, the Act does not specifically address the situation in which multiple ANDA Applicants are challenging the same patents.

What happens, then, when one Applicant's litigation is still ongoing and another Applicant receives a court decision that the patent is invalid or not infringed? Under prior law, FDA interpreted similar statutory language to mean that (1) in the case of invalidity, the 30-month stay terminated upon a decision of any court that the patent is invalid but (2) in the case of non-infringement, the stay terminated only upon a decision of a court that the specific Applicant's product does not infringe the patent. Will the FDA continue to apply that approach or will it interpret the requirement for a decision of invalidity or non-infringement by "the district court" or "the court of appeals" to mean, in each case, the specific court presiding over the litigation between the NDA holder and the ANDA Applicant?

The uncertainty created by the ambiguity, and the resulting need for FDA guidance, may be illustrated by the following example:

Assume the following facts:

NDA product; Orange Book patents	First ANDA Applicants	Hatch-Waxman Certification	Litigation timelines (NDA holder brings patent infringement actions against Company X and Company Y in separate jurisdictions)
Product A	Company X	Company X: Paragraph IV certifications to all patents, alleging invalidity of Patents 1, 2 and non- infringement of Patents 3, 4	Company X: Month 18: District Court grants summary judgment of invalidity of Patent 1 Month 25: District Court holds that Patent 2 is invalid and that Patents 3 and 4 are not infringed by Company X's product
Patents 1-4 (All patents are listed in FDA's Orange Book prior to ANDA submission)	Company Y	Company Y: Paragraph IV certifications to all patents, alleging invalidity of Patents 1, 3 and non- infringement of Patents 2, 4	Company Y: Month 12: District Court grants summary judgment of invalidity of Patent 3 Month 20: District Court holds that Patent 1 is invalid and that Patents 2 and 4 are not infringed by Company Y's product

On these facts, when would the 30-month stay of the final approval of Generic Company X's ANDA terminate? In month 18, as a result of the district court's grant of Generic Company X's motion for summary judgment of invalidity of Patent 1? In month 25, as a result of the decision of the district court that Patent 2 is invalid and that Patents 3 and 4 are not infringed by Generic Company X's product? In month 12, as a result of the district court's grant of Generic Company Y's motion for summary judgment of invalidity of Patent 3? Or in month 20, as a result of the decision of the district court that Patent 1 is invalid and that Patents 2 and 4 are not infringed by Generic Company Y's product?

Forfeiture of the 180-Day Exclusivity Period (21 U.S.C. § 355(j)(5)(B)(iv); 21 U.S.C. § 355(j)(5)(D)): General Request for Guidance. The new forfeiture provisions are extremely complex and represent a substantial change from the law that was in effect prior to the adoption of

the Act. Read broadly, the forfeiture provisions could significantly diminish the number of first-to-file opportunities that result in a period of marketing exclusivity for the First ANDA Applicant. If this is the effect of those provisions, many companies will have to reassess and revalue their development portfolios as well as their future development strategies.

It is very important, therefore, to understand how FDA intends to interpret the forfeiture provisions. As part of any industry guidance, it is requested that FDA apply those provisions to several examples to illustrate the impact of the Act. To assist FDA in that effort, the following hypothetical fact scenarios are proposed for the agency's consideration:

1. Product A

First Applicant's ANDA filing date	Orange Book Patents	Patent Exp. Dates	Patent Certification	Other Hatch-Wax. Excl.	HW Excl. Exp. Dates
11.15.06 (NCE minus 1 yr.)	Compound (basic)	3.30.13	Scenario (1): Par. III Scenario (2): Par. IV	NCE	11.15.07
	Compound (sub-generic and species)	10.30.12	Scenarios (1) and (2): Par. IV	Indication	8.30.07

Scenarios

First ANDA applicant submits a Paragraph III certification to the basic compound patent and a Paragraph IV certification to the sub-generic/species patent. NDA holder sues First ANDA applicant with respect to its Paragraph IV challenge; applicant wins the challenge; date of final decision of invalidity: 11.15.10. Applicant did not challenge the basic compound patent and, therefore, cannot go to market until expiration of that patent on 3.30.13.

First ANDA applicant submits Paragraph IV certifications to both patents; NDA holder sues applicant with respect to both challenges; applicant wins challenge on the sub-generic/species patent but loses the challenge on the basic compound patent; date of final decision of (i) invalidity of the

sub-generic/species patent and (ii) validity and infringement of the basic compound patent: 11.15.10. Because the basic compound patent was upheld and determined to be infringed, First ANDA applicant cannot go to market prior to expiration of that patent on 3.30.13.

2. Product B

First Applicant's ANDA filing date	Orange Book Patents	Patent Exp. Dates	Patent Certification	Other Hatch-Wax. Excl.	HW Excl. Exp. Dates
6.30.06	Compound (basic)	10.30.06	Scenarios (1) and (2): Par. III	New Product	8.30.05
	Compound (polymorph)	11.30.19	Scenarios (1) and (2): Par. IV		
	Method of Use	11.30.15	Scenarios (1) and (2): Par. III		
	Formulation/Composition	11.30.18	Scenarios (1) and (2): Par. IV		

Scenarios

NDA holder sues First ANDA applicant with respect to all Paragraph IV challenges; applicant wins challenges; date of final decision of invalidity/non-infringement: 6.30.10. Cannot launch prior to 11.30.15 (because a Paragraph III certification was filed on the method of use patent)

NDA holder does not sue First ANDA applicant within the Hatch-Waxman 45-day period (thus, no 30-month stay). Again, applicant cannot launch prior to 11.30.15 because a Paragraph III certification was filed on the method of use patent

3. Product C

First Applicant's ANDA filing date	Orange Book Patents	Patent Exp. Dates	Patent Certification	Other Hatch-Wax. Excl.	HW Excl. Exp. Dates
10.30.07 (NCE minus 1 yr.)	Compound (basic)	6.15.16	Scenarios (1) and (2): Par. IV	NCE	10.30.08
	Formulation/Composition	9.30.14	Scenarios (1) and (2): Par. IV		

Scenarios

NDA holder sues First ANDA applicant with respect to all Paragraph IV challenges; applicant wins challenge on formulation patent; loses challenge on compound patent; date of final decision of (i) invalidity/non-infringement of formulation patent and (ii) validity (and infringement) of compound patent: 10.30.11. As a result of the final decision upholding the compound patent and the determination of infringement, applicant cannot launch prior to the 6.15.16 expiration date of that patent

NDA holder sues First ANDA applicant with respect to the compound patent only; applicant loses challenge; date of final decision is 10.30.11. As a result of the final decision upholding the compound patent and the determination of infringement, cannot launch prior to the 6.15.16 expiration date of that patent

4. Product D

First Applicant's ANDA filing date	Orange Book Patents	Patent Exp. Dates	Patent Certification	Other Hatch-Wax. Excl.	HW Excl. Exp. Dates
2.01.05	Compound (basic)	7.30.10	Scenarios (1) and (2): Par. III Scenario (3): Par. IV	NCE	2.01.06
	Formulation/Composition	12.15.17	Scenarios (1)-(3): Par. IV	Indication	4.30.06

Scenarios

NDA holder sues First ANDA applicant with respect to its Paragraph IV challenge to the formulation patent; applicant wins the challenge; date of final decision of invalidity/ non-infringement: 2.01.09. Applicant did not challenge the basic compound patent and, therefore, cannot launch prior to the expiration of that patent on 7.30.10

NDA holder does not sue First ANDA applicant within the Hatch-Waxman 45-day period (thus, no 30-month stay). Again, applicant cannot launch prior to 7.30.10 because it did not challenge the basic compound patent

Assume instead that First ANDA applicant also files a Paragraph IV certification against the basic compound patent; applicant loses that challenge but, because of the additional complications associated with a validity challenge to the compound patent, the final decision of (i) invalidity/non-infringement of the formulation patent and (ii) validity (and infringement) of the compound patent is not rendered until 6.30.10. Again, because the applicant lost its challenge to the compound patent, it cannot launch prior to the 7.30.10 expiration of that patent

Product E

First Applicant's ANDA filing date	Orange Book Patents	Patent Exp. Dates	Patent Certification	Other Hatch-Wax. Excl.	HW Excl. Exp. Dates
6.30.05	Compound (basic)	6.30.08	Scenarios (1) and (2): Par. III	Indication	8.15.06
	Formulation/Composition	12.06.13	Scenarios (1) and (2): Par. IV		
	Method of Use	11.30.15	Scenarios (1) and (2): Par. IV		
	Formulation/Composition	1.30.18	Scenarios (1) and (2): Par. IV		
	Compound (polymorph)	11.30.15	Scenarios (1) and (2): Par. IV		

Scenarios

NDA holder sues First ANDA applicant with respect to all Paragraph IV challenges; applicant wins those challenges; date of final decision of invalidity/non-infringement: 6.30.09

NDA holder sues First ANDA applicant with respect to all of its Paragraph IV challenges; Applicant wins the challenge on the formulation and method of use patents; loses the challenge on the polymorph patent; date of final decision of invalidity/non-infringement of the formulation and method of use patents and validity (and infringement) of the polymorph patent: 6.30.09. Because of the final adverse decision on the polymorph patent, applicant cannot launch prior to the 11.30.15 expiration date of that patent

Forfeiture of the 180-Day Exclusivity Period: Failure to Market Provisions (21 U.S.C. § 355(j)(5)(D)(i)(I)). Clarification by FDA of the following failure to market provisions would be appreciated.

Failure to Market Within 30 Months After the Date of ANDA Submission (21 U.S.C. § 355(j)(5)(D)(i)(I)(aa)(BB)). The Act provides that if a first applicant (or another applicant which has received tentative approval) is not sued by the NDA holder (or the patent owner), or does not bring a declaratory judgment action, with respect to any of the patents which qualify the first applicant for the 180-day exclusivity, the first applicant forfeits its claim to 180-days exclusivity if it fails to market its drug within 30 months after the date of submission of its ANDA.

Of course, an applicant cannot commercialize its product if the approval of its application has not been made effective within that 30-month period. In that regard, the Act is silent as to whether the forfeiture is stayed if the failure to market within the 30-month period is caused by FDA's failure to approve the ANDA as a result of a change in or a review the requirements for approval of the application imposed after the date on which the ANDA is filed.

In a related context, the Act provides that the 180-day exclusivity is forfeited if the first applicant fails to obtain tentative approval of its ANDA within 30 months after the date on which the application is filed (21 U.S.C. § 355(j)(5)(D)(i)(IV)). In that case, however, the Act makes clear that forfeiture would not occur if such "failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed."

There is no logical basis for distinguishing between final approval and tentative approval for these purposes. For example, it has become commonplace for NDA holders to file Citizen Petitions to challenge the standards for determining bioequivalence of a generic version of the NDA drug or to raise other questions with respect to the safety or efficacy of such generic drugs. Such Petitions can be submitted at any time and, in fact, are often submitted shortly before a generic applicant expects to receive final approval of its ANDA. Since a Citizen Petition must be carefully considered by FDA, it invariably results in a substantial delay in approval of the ANDAs.

Similarly, if a Citizen Petition is denied, the petitioner may apply to the courts for injunctive relief to prevent the launch of the generic product or to have the approval of the ANDA rescinded on the grounds, for example, that FDA acted arbitrarily and capriciously in denying the Petition. This may occur before or after the FDA grants final approval to the first applicant's ANDA. If the court grants the requested relief, the first applicant will be prevented from marketing its product until the litigation is finally resolved, even if approval of its ANDA has been made effective by FDA.

As in the case of tentative approval, the first applicant should not have to suffer the extreme remedy of forfeiting its 180-days exclusivity if it is prevented from marketing its product because the agency

is evaluating a Citizen Petition, a court has enjoined the launch while litigation between FDA and the petitioner is ongoing or the agency is otherwise re-visiting the requirements for approval of the ANDA.

It is requested, therefore, that FDA confirm that a first applicant's claim to 180-days exclusivity is not forfeited if the failure to market its product within 30 months following the submission of the applicant's ANDA is a result of a change in or a review of the approval requirements imposed after the applicant submits its ANDA.

Failure to Obtain Tentative Approval within 30 Months after the Date on which the ANDA is filed (21 U.S.C. § 355(j)(5)(D)(i)(IV)). As noted above, the Act provides that the first Applicant forfeits its claim to 180-days exclusivity if it “fails to obtain tentative approval of its application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.” However, the statute provides no guidance as to what constitutes “a change in or a review of the requirements for approval”. Given the potentially significant adverse impact of this forfeiture event, such guidance from FDA would be extremely useful.

1. It is requested that FDA confirm that the first applicant's claim to 180-days exclusivity will not be forfeited so long as its ANDA would have been eligible for tentative approval within the specified 30-month period based on the requirements for approval that were in place at the time that the first applicant submitted its application. For these purposes, as in the case of the 30-month stay provisions (21 U.S.C. § 355(j)(5)(B)(iii)), the relevant application should be the original ANDA; amendments should be excluded.

As part of any such guidance, FDA should identify specific examples of the types of subsequent “changes” in or “reviews” of the requirements for approval which would stay the forfeiture of the 180-day exclusivity. It is proposed that any such list should include changes in or review of the following (whether initiated by the agency or requested in a Citizen Petition or similar request for agency action):

- ?? Requirements for establishing bioequivalence to the reference listed drug
- ?? Product specifications (including specifications relating to excipients and residual solvent levels)
- ?? Product characterization requirements

- ?? Product labeling (including consideration of proposed carve-outs of protected portions of the labeling for the reference listed drug which were added to the reference labeling after the submission of the ANDA)
- ?? USP specifications
- ?? Requirements relating to the active ingredient(s) (including identification of the “active” components of the product)
- ?? Current Good Manufacturing Practices (cGMPs), to the extent that compliance with the cGMPs which are changed or under review is a condition to receiving tentative approval of the application

2. The Act is also silent as to the effect of the “change in or review of the requirements for approval of the application”. Does it result in the complete elimination or only a stay of the forfeiture event? A stay would appear to be more consistent with the objectives of assuring that the first applicant (i) markets its product at the earliest opportunity but (ii) is not penalized for its inability to launch because of delays caused by changes that were made or were under consideration after its application was submitted. It is requested that FDA confirm that it agrees with this assessment and that it will stay the forfeiture of the first applicant’s right to 180 days’ exclusivity in the event of a change in or review of the requirements for approval of the application. Alternatively, if FDA does not believe that a stay is the appropriate remedy, guidance would be appreciated as to how the agency intends to apply the forfeiture provision.

Assuming that FDA intends to stay the forfeiture of exclusivity, it is recommended that the stay should be in effect (a) in the case of a change in the requirements for approval, for the length of time that it takes the first applicant to comply with the changes and for the agency to confirm compliance; and (b) in the case of a review of the requirements for approval, for the length of time that the requirements are under review plus, if the review results in a change in requirements, the time that it takes for the first applicant to comply and for the agency to confirm compliance.

The effect of a stay can be illustrated by the following example: assume that (w) 20 months following the first applicant’s submission of its ANDA, a Citizen Petition is submitted to FDA requesting a change in the requirements for establishing bioequivalence to the reference listed drug; (x) 10 months following the receipt of the Citizen Petition, FDA issues its final response in which it agrees with the petitioner and imposes new bio-study requirements on the First ANDA applicants;



(y) it takes the first applicant 12 months to design the new studies, perform the testing and submit the amendment to its ANDA in compliance with the changes required by the agency; and (z) 6 months following the receipt of the amendment, FDA, applying the new standards, makes a determination that the first applicant's product is bioequivalent to the reference listed drug.

In that event, it is submitted, and requested that FDA confirm, that the forfeiture event should be stayed for a period of 28 months, which is the delay time resulting from FDA's review of, and its changes in, the requirements for approval of the first applicant's ANDA.

Thank you for the opportunity to submit these comments. As you can see, Sandoz Inc. believes that there are important regulatory decisions that the FDA must make in order to properly administer these changes in the law.

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