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CITIZEN PETITION

The undersigned, on behalf of Celgene Corporation (“Celgene”), submits this petition under Sections 502, 505, and 527 of the Federal Food, Drug, and Cosmetic Act, among other provisions of law. Celgene respectfully requests that the Commissioner of Food and Drugs (“Commissioner”) refrain from approving any application for a generic thalidomide product. Such applications raise unacceptable safety risks. Approval at this time would also violate Celgene’s orphan drug exclusivity. Alternatively, if the Commissioner were to decide to approve an application for a generic thalidomide product, then Celgene requests that the requisite restricted distribution program for the generic thalidomide product limit marketing and distribution to ensure patient safety consistent with Celgene’s program and to be consistent with Celgene’s orphan drug exclusivity.

Fifty years after the Food and Drug Administration (“FDA”) first refused to approve thalidomide in the United States, the FDA once again faces an application for thalidomide that creates unacceptable safety risks. Specifically, Barr Laboratories, Inc. (“Barr”) is seeking approval for the first generic thalidomide product under ANDA 78-505 for treatment of the cutaneous lesions of erythema nodosum leprosum (“ENL”). As detailed below, the risks associated with a generic thalidomide product greatly outweigh any benefits from such product.

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Thalidomide has been shown to have important benefits when used appropriately. Celgene's current System for Thalidomide Education and Prescribing Safety ("S.T.E.P.S.®") program tightly controls the distribution of Celgene's thalidomide product, Thalomid®, through multiple validated computer databases. It requires registration by patients, prescribers, and pharmacists. In fact, each prescription must receive an authorization number and a confirmation number before the drug can be dispensed. Due to Celgene's efforts, more than 150,000 patients safely have received thalidomide. But the safe distribution of thalidomide cannot and should not be taken for granted. Even today, babies are born with severe birth defects from the unsafe use of thalidomide in foreign countries, including countries that have attempted to use risk management measures.¹

More specifically, Barr's application raises serious questions of safety related to: (1) the potential impact of having multiple restricted distribution programs for thalidomide; (2) whether Barr can and will dedicate the resources necessary to adequately implement its own restricted distribution program; and (3) the labeling for a generic thalidomide product, which would have to omit important information protected by Celgene's orphan drug exclusivity.

In light of its history and teratogenicity, thalidomide is not like any other FDA approved drug. It takes *only one* thalidomide capsule *regardless of strength* to cause a birth defect. Accordingly, thalidomide requires the highest level of manufacturing diligence to prevent any mistakes, such as the cross-contamination of active ingredients. As detailed below, Celgene believes that the risks associated with a generic thalidomide product greatly outweigh any reasons for otherwise approving a generic product.

In addition to the safety issues, FDA's approval of a generic thalidomide product would violate Celgene's orphan drug exclusivity for the multiple myeloma indication. Thalomid® is

¹ For example, Brazil restricts the distribution of thalidomide through a nationally-run program that requires pregnancy testing and contraceptive measures. However, despite Brazil's restricted distribution program, there have been several babies born recently in Brazil with birth defects due to thalidomide. *See, e.g., "No Role for Thalidomide in Leprosy,"* WHO Leprosy Team, World Health Organization (May 12, 2003) (available at <http://www.paho.org/English/AD/DPC/CD/thalidomide.htm>) (Tab 1) at 1 ("Today, a new group of victims are suffering in many countries, particularly in Brazil, which also continues to manufacture and export thalidomide on a large scale").

indicated for the treatment of ENL and multiple myeloma. Celgene earned orphan drug exclusivity for multiple myeloma, which expires in 2013. The patient population for ENL is vanishingly small. Indeed, there are currently just over 100 patients with ENL in the United States who are known to take Thalomid[®], representing approximately one half of 1% (0.5%) of Thalomid[®] prescriptions. Celgene provides free Thalomid[®] to about half of those ENL patients through Celgene's needs-based Patient Assistance Program.

Quite obviously, the fact that a generic company is apparently willing to manufacture and market a product subject to an extensive and expensive restricted distribution program for a target population of approximately 50 patients indicates that the company is really seeking approval to distribute its product for the much larger and protected multiple myeloma indication. Presumably, Barr's restricted distribution program would not exclude multiple myeloma. Barr will have complete control over who receives its product under its restricted distribution program. Without completely excluding multiple myeloma from all of its conditions of use, Barr is essentially seeking approval to market its product in violation of Celgene's exclusivity. In fact, Barr recently gave a presentation to its investors identifying the market for thalidomide to include all patients, including those with multiple myeloma.²

If FDA were to decide to approve Barr's ANDA for generic thalidomide, then FDA should require Barr to exclude multiple myeloma from its restricted distribution program because that indication will be excluded from Barr's proposed indication and is protected by Celgene's orphan drug exclusivity. This would protect the integrity of Celgene's orphan drug exclusivity without harming the competing goal of making generic drugs available under the Hatch-Waxman Act. For FDA to approve the product for ENL only, while allowing Barr to actively authorize the distribution of generic thalidomide to multiple myeloma patients under its restricted distribution program, would be an improper application of the laws providing for the approval of generic drugs, as well as of the laws granting orphan drug exclusivity. Furthermore, enabling this activity undermines the spirit of the orphan drug laws and would discourage research and development of products for orphan indications.

² Barr Pharmaceuticals, Inc., Generic and Proprietary Pharmaceuticals, Investor Presentation July 2007 (available at <http://phx.corporate-ir.net/phoenix.zhtml?c=60908&p=irol-presentations>) (slide attached at Tab 2).

A. ACTION REQUESTED

1. FDA should refrain from approving any application for a generic thalidomide product, including Barr's ANDA No. 78-505, because an application for generic thalidomide raises unacceptable safety risks and violates Celgene's orphan drug exclusivity.

2. Alternatively, if FDA were to decide to approve an application for a generic thalidomide product, then FDA should (a) require the application for generic thalidomide to be subject to the same conditions of approval applied to Thalomid[®] under Subpart H of 21 C.F.R., Part 314, and (b) prohibit the restricted distribution program for the generic thalidomide product from actively authorizing prescriptions for multiple myeloma and registering patients with multiple myeloma and oncologists in violation of Celgene's orphan drug exclusivity.

B. STATEMENT OF GROUNDS

I. BACKGROUND

A. History of Thalidomide

From its tragic past to the unprecedented conditions put on its approval, thalidomide is clearly an exceptional drug. The mere mention of its name recalls images of severely disfigured babies. Due to its severe risks (unknown at the time), thalidomide was responsible for one of the worst public health tragedies in modern times. Thousands of malformed babies resulted from fetal exposure to thalidomide during the 1960s. Despite its inauspicious history, one company, Celgene, was willing to look beyond thalidomide's notoriety and invest the necessary resources to safely bring thalidomide to the U.S. market for the benefit of the public health. As a result of Celgene's significant efforts, thalidomide is currently used to treat patients suffering from severe and often fatal diseases, such as multiple myeloma.

Once unimaginable, thalidomide's reemergence has undoubtedly contributed greatly to the public health. However, the safe use of thalidomide cannot be taken for granted. The thalidomide molecule marketed today is the same molecule that was marketed outside of the United States in the 1960s. The difference today is that Celgene has conceived of, developed,

and implemented an unprecedented restricted distribution program to ensure the safe use of its product. Without Celgene's devotion to safety, the risks associated with thalidomide would still be unacceptable.

Thalidomide had its beginnings in Europe during the 1950s. With a paucity of clinical safety and effectiveness data, thalidomide was marketed by Chemie Grunenthal in Germany as an over-the-counter sedative to treat insomnia and to reduce the nausea associated with pregnancy.³ By 1960, thalidomide had been introduced in 46 countries, but not the United States. The drug was a huge success due in large part to the marketing of Chemie Grunenthal, which promoted the drug as nontoxic and completely safe for pregnant women.⁴

In the United States, the Richardson-Merrell Co. submitted an application to market thalidomide as an over-the-counter sedative in 1960. At that time, the governing drug approval statute required only proof of safety, but not of effectiveness. The application was assigned to Frances Kelsey, M.D., Ph.D., a new FDA reviewer. From the start, Dr. Kelsey was critical of the clinical evidence supporting the application, particularly with respect to toxicity and fetal safety. She repeatedly requested additional data from the company, especially regarding reports of peripheral neuritis. In response, the company submitted clinical reports that "were more in the nature of testimonials."⁵ Although under tremendous pressure to approve the drug already used worldwide, Dr. Kelsey never wavered in her commitment to the public health. She steadfastly refused to approve the drug.

Around 1961, European physicians began reporting a substantial and unexplained increase in the number of deformed babies. The birth defects included abnormally short limbs, with toes extruding directly from the hips and flipper-like arms (*i.e.*, phocomelia), and malformed internal organs, eyes, and ears. Ultimately, German and Australian doctors linked the

³ Silverman, W., "The Schizophrenic Career of a 'Monster Drug,'" *Pediatrics* 2002; 110; 404-406 (Tab 3).

⁴ Burkholz, H., "Giving Thalidomide A Second Chance," *FDA Consumer Magazine* (September - October 1997) (available at http://www.fda.gov/fdac/features/1997/697_thal.html).

⁵ "Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History," *FDA Consumer Magazine* (March - April 2001) (available at http://www.fda.gov/fdac/features/2001/201_kelsey.html).

birth defects to thalidomide. Subsequently, Germany and the other countries pulled thalidomide from the market. By that time, more than 10,000 children in 46 countries were believed to have been born with thalidomide-related birth defects.⁶

Due to Dr. Kelsey's foresight and caution, thalidomide was never marketed in the United States. Indeed, in 1962, President John F. Kennedy awarded Dr. Kelsey the medal for Distinguished Federal Civilian Service, our Nation's highest civilian honor. Additionally, the near tragedy compelled Congress to tighten the drug approval laws. In particular, Congress passed the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act ("FDCA").⁷ These amendments dramatically increased FDA's control over drug testing. They also required companies to demonstrate that a drug was effective before it could be approved.

Although withdrawn from the market internationally, thalidomide eventually reemerged as a drug with potential benefit for patients with serious illness. In 1965, an Israeli dermatologist treating patients with leprosy made a chance observation.⁸ Leprosy is an infectious disease that affects the skin, nerves, and respiratory tract. A subset of patients with one particular form of leprosy, lepromatous, may develop an inflammatory complication called erythema nodosum leprosum (ENL). ENL is an acute reaction in patients with lepromatous leprosy. It causes severe skin lesions and associated systemic symptoms, such as neuritis and fever. To comfort his leprosy patients, who particularly had trouble sleeping, the Israeli doctor prescribed thalidomide as a sedative.⁹ Surprisingly, he noticed that patients with ENL, within several days of starting thalidomide, had improved neuritis and skin lesions. Subsequently, many controlled studies showed that thalidomide was effective in treating ENL manifestations.¹⁰ The World

⁶ *Id.*

⁷ *Id.*

⁸ See Woodcock, J., Supervisory Review of NDA 20-785 (Thalomid[®]) (July 7, 1998) (available at <http://www.fda.gov/cder/news/thalinfo/20785medr.htm>) ("Thalomid[®] Supervisory Review") at 1.

⁹ Silverman, W., "The Schizophrenic Career of a 'Monster Drug,'" *Pediatrics*[®] 2002; 110; 404-406 (Tab 3).

¹⁰ Thalomid[®] Supervisory Review at 1.

Health Organization even recommended thalidomide as a treatment for ENL, a position that has since been reversed.¹¹

In the United States, the National Hansen's Disease Center ("the NHDC") and the U.S. Public Health Service began to make thalidomide available to patients with ENL through an Investigational New Drug ("IND") application.¹² The NHDC, however, had a problem obtaining a stable source of high quality product. It often had to compound a finished dosage form from bulk product. FDA helped make thalidomide available by testing bulk product.¹³ In the early 1990s, a doctor at the Rockefeller University in New York discovered that thalidomide modulates tumor necrosis factor-alpha (TNF- α) production. TNF- α is an important cytokine involved in many diseases. Ultimately, thalidomide was shown by additional researchers to possess immunomodulatory, anti-inflammatory, and anti-angiogenic properties.¹⁴ As such, thalidomide showed great potential for the treatment of a wide variety of serious and life-threatening diseases, including cancer and AIDS-related conditions. As with the situation at the NHDC, the FDA cooperated with manufacturers to establish "single-patient" and "open protocol" INDs so that physicians could use investigational thalidomide.¹⁵ However, no company was willing to take responsibility at the time for bringing an approved version of thalidomide to the U.S. market.

Despite its best efforts, FDA had difficulty keeping up with the demand for thalidomide, and the underground and illegal use of thalidomide began to flourish. In particular, patients seeking relief began securing thalidomide through illegal buyers' clubs. Companies distributing

¹¹ Since Thalomid[®] was approved, the World Health Organization has reversed its position and now believes that the risks associated with thalidomide do not justify its approval for ENL. "No Role for Thalidomide in Leprosy," WHO Leprosy Team, World Health Organization (May 12, 2003) (Tab 1).

¹² Thalomid[®] Supervisory Review at 1.

¹³ *Id.*

¹⁴ Burkholz, H., "Giving Thalidomide A Second Chance," FDA Consumer Magazine (September - October 1997) (available at http://www.fda.gov/fdac/features/1997/697_thal.html).

¹⁵ *Id.*

illegal thalidomide repeatedly ignored FDA's warnings to stop.¹⁶ FDA began working to find a company willing to bring thalidomide to the U.S. market in a safe and responsible manner.

B. Celgene's Efforts To Establish Regulatory Control

At that point, Celgene, a small spin-off from the chemical company Celanese Corp., also began working to legitimize the use of thalidomide. With very little revenue and no pharmaceutical products, Celgene recognized an opportunity that would benefit both the public health and the company. Yet, even with FDA's general support and encouragement, the hurdles to bringing an approved thalidomide drug to market were immense. Celgene had to maneuver through scientific skepticism, a lack of financial backers, insurance problems, and the very real and emotional issue of thalidomide survivors who were understandably vehemently opposed to the marketing of any thalidomide product, under any circumstances.

Ultimately, Celgene submitted a New Drug Application (No. 20-785) for the use of thalidomide to treat ENL. Approximately 35 years after FDA first received Richardson-Merrell's application, FDA was once again considering an application for a thalidomide product. Could a drug that was so risky and had caused so much damage be safely marketed to the public? Due to FDA's concern about teratogenicity issues, the review of Celgene's application was not typical, and due to these same safety issues, neither should the review of the ANDA be typical.

The National Institutes of Health ("NIH") and the FDA sponsored a two-day open scientific workshop on the potential benefits and risks of a thalidomide product. The workshop included more than 50 presentations from FDA, NIH, Centers for Disease Control and Prevention ("CDC"), thalidomide victims associations, universities, AIDS groups, foreign countries, and Celgene.¹⁷ In addition to the workshop, there was a two-day meeting of FDA's

¹⁶ For example, in 1995, FDA sent a warning letter to LifeLink stating that "despite the agency's warnings, your organization continues the illegal distribution of thalidomide." FDA Warning Letter from S. Gray, FDA Office of Compliance, to D. Blanco, LifeLink (September 1, 1995); *see also* FDA Warning Letter from S. Gray, FDA Office of Compliance, to S. Cooper, PWA Health Group (September 1, 1995) ("despite the agency's requests . . . PWA Health Group has continued its illegal distribution of the drug [thalidomide]").

¹⁷ Thalidomide: Potential Benefits and Risks. An Open Public Scientific Workshop Sponsored by the National Institutes of Health and the Food and Drug Administration, September 9-10, 1997, Bethesda, Maryland (transcripts available at <http://www.fda.gov/cder/drug/Infopage/thalidomide/default.htm>).

Dermatologic and Ophthalmic Drugs Advisory Committee regarding Celgene's application. The meeting included more than 30 committee members, consultants, FDA staff, guest speakers, and Celgene representatives.¹⁸ At the end of meeting, the Advisory Committee voted 6-1 that thalidomide is effective for the treatment of the cutaneous lesions of ENL.¹⁹

Although the evidence supported the drug's effectiveness, thalidomide still posed a substantial safety risk due to its teratogenicity. Accordingly, Celgene developed an unprecedented, restricted distribution program to prevent any fetal exposure. As described below in detail, Celgene's S.T.E.P.S.[®] program is a closed system that tightly controls the distribution of Celgene's thalidomide product from beginning to end. Each patient, prescriber, and pharmacist must register in the program. No prescription may be dispensed without authorization and confirmation numbers.

On July 16, 1998, FDA approved Celgene's product, Thalomid[®] (thalidomide), for the treatment of ENL. Although the primary and secondary FDA reviewers concluded that Celgene's application should not be approved, they were overruled by FDA's Director of the Office of Drug Evaluation.²⁰ That decision was further supported by the then-Director of the Center for Drug Evaluation and Research.²¹ Along with the approval, Celgene earned a period of orphan drug exclusivity for ENL, which has since expired.

To ensure the safety of the product, FDA, for the first time, invoked the restricted distribution provisions under Subpart H of its regulations (21 C.F.R. § 314.520), which is directed to products with safety issues that cannot be addressed under ordinary approval conditions.²² In addition to Celgene's S.T.E.P.S.[®] program, FDA also formed a thalidomide

¹⁸ Forty-Seventh Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee, Center for Drug Evaluation and Research, Food and Drug Administration, September 4-5, 1997, Bethesda, Maryland (transcripts available at <http://www.fda.gov/cder/drug/Infopage/thalidomide/default.htm>).

¹⁹ Thalomid[®] Supervisory Review at 2.

²⁰ Office Director's Review Memorandum of NDA 20-785 by M. Weintraub, M.D. (September 19, 1997).

²¹ Thalomid[®] Supervisory Review.

²² "FDA Approves Thalidomide for Hansen's Disease Side Effect, Imposes Unprecedented Restrictions on Distribution," FDA Talk Paper (July 16, 1998); and Thalomid[®] Supervisory Review at 25.

response team to oversee postmarketing adverse event reporting and rapidly investigate any report of suspected fetal exposure.

On May 25, 2006, Celgene received FDA approval for the use of thalidomide in combination with dexamethasone for the treatment of patients with newly diagnosed multiple myeloma. Multiple myeloma is a fatal cancer of the plasma cells, which is characterized by excessive numbers of abnormal plasma cells in bone marrow and an overproduction of monoclonal immunoglobulins. It is the second leading blood cancer and affects approximately 70,000 people in the United States. As a result of this approval, Celgene earned orphan drug exclusivity for the multiple myeloma indication. That exclusivity expires in 2013.

C. Celgene's S.T.E.P.S.[®] Program Strictly Controls the Distribution of Thalomid[®]

1. The S.T.E.P.S.[®] Restricted Distribution Program

The distribution of Thalomid[®] is tightly controlled through Celgene's S.T.E.P.S.[®] ("System for Thalidomide Education and Prescribing Safety") program. The S.T.E.P.S.[®] system involves multiple participants and databases. Currently, the backbone of S.T.E.P.S.[®] is a performance-linked access system. It is comprised of a complex network of Oracle[®] database, fax, image storage, telecommunications, and Interactive Voice Response servers, not to mention the many full time employees dedicated to the facilitation of the program. The system tracks every aspect of the distribution of Thalomid[®] capsules from the manufacturer to the patient. The S.T.E.P.S.[®] program, which is specifically designed to prevent fetal exposure to Thalomid[®], involves participation from physicians, pharmacists, patients, Celgene, third party contractors, and FDA. Essentially, S.T.E.P.S.[®] comprises:

- (1) mandatory pregnancy testing,
- (2) mandatory birth control,
- (3) physician and patient education using videotapes, brochures, and other similar materials,²³

²³ See, e.g., Important Information for Men and Women Taking Thalomid[®] (thalidomide) Capsules; Celgene Patient Brochure (Tab 4).

- (4) mandatory prescriber, pharmacist, and patient registration,
- (5) mandatory patient informed consent and related certifications, and
- (6) controlled distribution.

In total, more than 175 Celgene employees work to implement S.T.E.P.S.[®], including over 50 employees solely dedicated to staffing the S.T.E.P.S.[®] service center described below.

The patient, prescriber, and pharmacist are all integral parts of the S.T.E.P.S.[®] system. They each must register in the program. Prescribers must return a registration card to Celgene committing them to comply with S.T.E.P.S.[®]. After registration, prescribers are provided with software to generate necessary forms, as well as patient education materials, including videotapes and brochures. With respect to pharmacies, the head pharmacist is responsible for registering in the program and for educating other staff members about the requirements of S.T.E.P.S.[®]. Patients register by completing informed consent forms. All of the registration information is tracked and coordinated by Celgene through multiple computer databases.

On an initial visit, a prescriber assigns a patient to one of six risk groups so that the patient may receive S.T.E.P.S.[®] material specific for the assigned risk group (*e.g.*, adult females of childbearing potential, adult males, female child, etc.). Patients then receive counseling and related written material regarding the risks and benefits of therapy and contraceptive use, including a patient brochure and/or videotape regarding the safe use of Thalomid[®]. Female patients of childbearing potential are required to use two forms of contraception, including one highly effective method (*e.g.*, oral contraceptives) and one effective method (*e.g.*, condom). The patient must use such contraception four weeks before therapy, during therapy, and for at least four weeks after therapy. Male patients are also counseled on birth control and are instructed to use a latex condom during intercourse. Furthermore, all patients are counseled not to give blood while taking Thalomid[®], and in addition, male patients are counseled not to donate sperm.

When a female patient is ready to initiate therapy, the prescriber must repeat the patient counseling and perform a pregnancy test. For women of childbearing potential, the pregnancy test must be performed within 24 hours of beginning therapy. Furthermore, such women must have a pregnancy test every week for the first four weeks of treatment, and then every four

weeks thereafter if their menstrual cycles are regular, or every two weeks if their menstrual cycles are irregular. Pregnancy testing and counseling are performed if a female patient misses her period or if there is an abnormality in menstrual bleeding. If a pregnancy does occur during treatment, the Thalomid[®] treatment is immediately discontinued. Any suspected fetal exposure must be reported immediately to FDA and Celgene. The patient is also directed to consult an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation.

Additionally, the prescriber provides a risk group specific informed consent form to the patient, which is generated using computer software supplied by Celgene. After the form is signed, it is faxed to Celgene. The patient is then registered into the S.T.E.P.S.[®] system. Subsequently, both the patient and the prescriber complete individual phone surveys that use an Interactive Voice Response (“IVR”) system. Before a prescription may be issued, the prescriber and patient must answer all of the IVR questions appropriately. When a response to the IVR survey signals an at-risk behavior (*e.g.*, pending or outdated pregnancy test), the prescriber or patient is transferred to a Celgene S.T.E.P.S.[®] intervention specialist for “real-time” intervention. *Celgene specialists are available seven days a week, 24 hours a day. Most issues are addressed within one day. The S.T.E.P.S.[®] program handles approximately 16,000 surveys, 20,000 calls, and 10,000 faxes a month.*

When both the patient and prescriber provide appropriate responses to the IVR survey, a Thalomid[®] prescription is “activated.” At that point, the prescriber may provide the patient with a prescription. The prescriber receives an authorization number from the IVR survey that is placed on the prescription. Without the authorization number, Thalomid[®] may not be dispensed. An activated prescription allows a pharmacist to call the IVR system, enter the authorization number for the prescription, and receive a confirmation number authorizing the pharmacist to dispense Thalomid[®]. The prescription may not be for more than a 28 day supply of Thalomid[®]. There are no refills. The prescription must be filled within seven days from the day it was issued. The IVR survey is completed again with each 28-day interval, except for adult females not of childbearing potential, who complete the survey every six months.

To further control distribution, Celgene directly ships Thalomid[®] to registered pharmacies. Direct shipping allows Celgene to compare the amount of Thalomid[®] shipped to the

amount that a specific pharmacy has been authorized to dispense. Additionally, Celgene's field organization visits every pharmacy that dispenses Thalomid[®] to provide education and training regarding S.T.E.P.S.[®]. When a pharmacy deviates from S.T.E.P.S.[®], Celgene's field organization returns to the pharmacy to provide re-education and training. Celgene has de-registered, and will continue to de-register, pharmacies for which re-training has proven ineffective, removing them from the S.T.E.P.S.[®] program.

2. Quality Assurance

In addition to the specific requirements of the S.T.E.P.S.[®] program, another important aspect to the success of the program is Celgene's quality control. The S.T.E.P.S.[®] program is administered under current Good Manufacturing Practices ("cGMP") conditions through a joint approach involving Celgene and FDA. In particular, Celgene formed a Product Risk Management Committee ("PRMC"), which has overall responsibility for monitoring and auditing the program. The PRMC is composed of senior Celgene personnel in the medical affairs, regulatory, drug safety, customer care, legal, sales, marketing, operations, and information technology departments, as well as industry experts in computerized databases, warehousing, distribution and manufacturing procedures, and compliance auditing. Illustrating the importance of the S.T.E.P.S.[®] program, the PRMC is chaired by Celgene's Senior Vice President of Regulatory Affairs and Pharmacovigilance.

The FDA is also involved in monitoring the S.T.E.P.S.[®] program. In particular, FDA has prohibited changes to the program without a prior approval supplement to the Thalomid[®] application. FDA also inspects monitoring sites and Celgene's records. As FDA explained in the Thalomid[®] approval letter:

CHANGES TO THE S.T.E.P.S. RESTRICTED DISTRIBUTION PROGRAM:

Please note that the June 8, 1998 S.T.E.P.S. restricted distribution program is an integral part of the approved NDA for this product and is an essential component of the terms of this NDA's approval by FDA for marketing this product in the United States. As such, any proposed change(s) in the S.T.E.P.S. program must be submitted to the FDA as a supplement to this NDA and any proposed change(s) must have FDA prior approval before implementation. Changing the

S.T.E.P.S. program without prior FDA approval may render the product misbranded and an unapproved new drug.

FUTURE INSPECTIONS:

In order to monitor the success of compliance with the restricted distribution provisions of this approval action, we intend to conduct inspections of the monitoring sites . . . as well as Celgene's records during the first quarter after product launch. We will meet with you to discuss the inspections within one month after completions of the inspections. Inspections and meetings with you will continue periodically thereafter as appropriate.

3. Success of the S.T.E.P.S.[®] Program

Celgene's development and implementation of the S.T.E.P.S.[®] program has been a success. Since inception there are currently more than 155,000 patients registered in the program, as well as over 36,000 pharmacies and 16,500 prescribers. The S.T.E.P.S.[®] program has successfully processed more than one million prescriptions of Thalomid[®] (approximately 100 million capsules) resulting in over 80,000 patient years of experience. In contrast to other risk management plans discussed below that seek to accomplish the same goal as S.T.E.P.S.[®], there have been no significant failures or implementation problems related to S.T.E.P.S.[®]. As summarized in a published research paper by FDA employees, "[t]he S.T.E.P.S. programme has been successful in preventing fetal exposure to thalidomide."²⁴ However, it would be naïve to conclude that the safe distribution of thalidomide is easily achieved based on Celgene's safety record. Failure to appreciate the difficulty of actually implementing and managing an appropriate restricted distribution program can result in a thalidomide birth in the U.S., which would have serious consequences for FDA, Celgene, and most importantly, the patients.

D. Celgene's Goal of a "Safer Thalidomide"

No company is more aware of the risks associated with marketing thalidomide than Celgene. Accordingly, Celgene has invested a significant portion of its revenue from Thalomid[®] in researching and developing new and safer treatments. Indeed, until 2006, Celgene was still operating at a cumulative net loss. Celgene has stated that a primary goal is to develop immune

²⁴ Uhl et al., "Thalidomide Use in the US: Experience with Pregnancy Testing in the S.T.E.P.S.[®] Programme," Drug Safety 29(4):321-329 (2006) (Tab 5).

modulating drugs based on the biologic activity of thalidomide, but without the teratogenicity risk. And, indeed, Celgene has already received marketing approval from FDA for an immune modulating compound, Revlimid® (lenalidomide), and continues the development of additional new molecules.

Similar to Thalomid®, Celgene distributes Revlimid® under a restricted distribution program called RevAssist®. As the innovator of such restricted distribution plans, safety is an integral part of Celgene's corporate culture. In many ways, the survival of the company depends on the successful implementation of its novel restricted distribution plans. There is simply no room for error. As a stark reminder of the constant risks, and as noted above, thalidomide babies are still being born even today in foreign countries that do not have programs that are as detailed and as effectively implemented as Celgene's S.T.E.P.S.®²⁵

Recently, Celgene was honored for its innovation and overall contribution to the public health. Specifically, the founder of the group from Celanese that spun out to form Celgene, and its current CEO and Chairman, received the Chemists' Clubs' Winthrop-Sears Award for 2006. That award recognizes entrepreneurs who have contributed to "the vitality of the chemical industry and the betterment of mankind."²⁶

II. ARGUMENT

A. Generic Thalidomide Raises Unacceptable Safety Issues

1. FDA May Not Approve an Abbreviated New Drug Application When There is a Reasonable Basis to Conclude that the Product May Be Unsafe

The drug approval process is intended to provide safe and effective drug products to the public. As no product is completely risk-free, safety is defined in terms of a product's risks compared to its benefits. As FDA has explained:

²⁵ See "No Role for Thalidomide in Leprosy," WHO Leprosy Team, World Health Organization (May 12, 2003) (Tab 1) ("Today, a new group of victims are suffering in many countries, particularly in Brazil, which also continues to manufacture and export thalidomide on a large scale").

²⁶ Celgene Founder Sol J. Barer to Receive 2006 Winthrop-Sears Award from the Chemists' Club of New York (March 27, 2006) (available at http://www.chemheritage.org/press/pr_06_mar_27.htm) (Tab 6).

[A] product is considered to be safe if the clinical significance and probability of its beneficial effects outweigh the likelihood and medical importance of its harmful or undesirable effects. In other words, a product is considered safe if it has an appropriate benefit-risk balance for the intended population and use.²⁷

The requirement that a product be safe applies to every product - innovator and generic - on an individual basis. “It is critical to FDA’s decision on product approval that a product’s underlying risks and benefits be adequately assessed during the premarketing period.”²⁸ FDA has indicated that it will consider an ANDA product unsafe and refuse to approve the ANDA if there is a reasonable basis to conclude that the ANDA raises serious questions of safety.²⁹ For example, FDA may not approve an ANDA when “there is a *reasonable basis* to conclude that one or more of the inactive ingredients of the proposed drug or its composition *raises serious questions of safety or efficacy*.”³⁰ Furthermore, FDA has noted that the ANDA disapproval standards are consistent with the ANDA withdrawal standards, and FDA may withdraw an ANDA “whenever there is a reasonable basis to conclude that a drug is unsafe even if the agency lacks proof that the drug is unsafe.”³¹ Thus, FDA should not approve an ANDA when there is a reasonable basis to conclude that the drug may be unsafe. The statute does not require *proof* that an ANDA product is unsafe. Rather, the mere fact that an ANDA raises serious questions of safety is sufficient to prevent the ANDA from being approved.

A reference product is shown to be safe through substantial clinical trials and carefully worded labeling. By contrast, a generic product generally is deemed to be safe through a demonstration that the generic product (i) is bioequivalent and pharmaceutically equivalent (*e.g.*, has the same active ingredient, route of administration, dosage form, and strength) to the reference product, and (ii) has the same labeling as the reference product. By demonstrating equivalence, the generic product is presumed to have the same risk/benefit analysis as the reference product.

²⁷ FDA Guidance for Industry: Development and Use of Risk Minimization Action Plans (March 2005) at 4.

²⁸ FDA Guidance for Industry: Premarketing Risk Assessment (March 2005) at 5.

²⁹ 21 C.F.R. § 314.127(a)(8).

³⁰ *Id.* (emphasis added).

³¹ Abbreviated New Drug Application Regulations (Final Rule), 57 Fed. Reg. 17,950, 17,969 (April 28, 1992).

Here, the presumption of safety does not apply to a generic thalidomide product. Due to the unique circumstances surrounding Thalomid[®], an application for a generic thalidomide product raises serious questions of safety and should not be approved for the reasons detailed below.

2. Multiple Thalidomide Restricted Distribution Programs Raise Important Safety Issues Relating to the Distribution of Thalidomide

(a) Increased Risk of Confusion and Medication Errors

As described above, S.T.E.P.S.[®] is a complicated interaction of multiple parties and databases. It is a proprietary program developed and administered by Celgene for the specific purpose of distributing Thalomid[®]. The risks associated with thalidomide require that each prescription and capsule be tracked and controlled from beginning to end. The underlying principle of S.T.E.P.S.[®] is that each prerequisite event must be confirmed before the next event may occur. As such, S.T.E.P.S.[®] is a closed program specifically linked to Thalomid[®]. The prescription authorization and confirmation numbers; registered prescribers, patients, and pharmacists; pregnancy and IVR data; and drug quantity tracking all relate to Thalomid[®].

It is inconceivable that Barr or another generic applicant would be allowed to market a generic thalidomide product without being required to use the same type of restricted distribution program that was so essential to the approval of Thalomid[®] and is so integral to its labeling. FDA would have to require the conditions of approval for Barr's application, as well as any other generic thalidomide application, to include a S.T.E.P.S.[®]-like risk management plan and would have to be certain that the implementation of that program provided the same level of safety afforded by Celgene's implementation of S.T.E.P.S.[®].

Thalidomide was approved under Subpart H. FDA has determined that it is safe only when distributed in accordance with a carefully conceived GMP risk management plan (*e.g.*, S.T.E.P.S.[®], as referenced and described in the Thalomid[®] labeling). In addition, a generic thalidomide product would have to have the same labeling as Thalomid[®] (except for differences discussed below) and show that its proposed conditions of use were previously approved for

Thalomid[®].³² For FDA to approve a generic thalidomide product without a risk management plan equivalent to that of Thalomid[®] is unimaginable, as it would not only be entirely irresponsible from a public health standpoint, but it would also be arbitrary and capricious, and violate the established administrative law principle requiring similarly situated products to be treated similarly.³³ Accordingly, consistent with the S.T.E.P.S.[®] program, Barr would also have to track each generic thalidomide prescription and capsule.

But the mere existence of multiple risk management plans linked to specific drug products creates an increased risk of confusion and medication errors. As FDA stated with respect to the initial risk management plans for the drug isotretinoin, “[t]he multiple programs created confusion and the concern that patients would not receive appropriate counseling and testing to prevent the possibility of birth defects.”³⁴

Furthermore, the patients, prescribers, and pharmacists bear a heavy burden with respect to implementing restricted distribution programs. The S.T.E.P.S.[®] program creates a complex and demanding process. Having an additional thalidomide system would compound the confusion and burdens associated with thalidomide risk management and make it more likely that the system would be compromised. Prescribers and pharmacists may stop distributing thalidomide, and patients may circumvent the system by finding alternative sources. This risk is heightened due to the fact that FDA generally has limited resources and authority to enforce compliance with risk management plans by patients, prescribers, and pharmacists.³⁵

³² 21 U.S.C. § 355(j)(2) and (4).

³³ *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 28 (D.D.C. 1997) (“The disparate treatment of functionally indistinguishable products is the essence of the meaning of arbitrary and capricious.”).

³⁴ “FDA Announces Enhancement to Isotretinoin Risk Management Program,” FDA Talk Paper (November 23, 2004) (available at <http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01328.html>); see also Testimony of J. Lindstrom, Medical Officer, FDA Division of Dermatologic and Dental Drug Products; Drug Safety and Risk Management Advisory Committee in Joint Session with the Dermatologic and Ophthalmic Drugs Advisory Committee (February 26, 2004) at 44 (available at <http://www.fda.gov/ohrms/dockets/ac/04/transcripts/4017T1.htm>).

³⁵ See New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58,942, 58,953 (December 11, 1992) (“[T]he burden is on the applicant to ensure that the conditions of use under which the applicant’s product was approved are being followed.”).

(b) The High Likelihood of Generic Substitution Would Undermine Both Restricted Distribution Programs

It is unclear how plans like S.T.E.P.S.[®], which control the distribution of each capsule from beginning to end, could operate safely in light of product substitution. A generic product that is therapeutically equivalent to the reference product is often substituted for the reference product by a pharmacist. In fact, some states even *require* substitution. However, a pharmacist could only substitute generic thalidomide by circumventing the risk management requirements. As the generic risk management program would have no information regarding the patient, prescription authorization and confirmation numbers for the generic thalidomide product could not be issued. In that situation, a pharmacist might simply circumvent risk management requirements and dispense generic thalidomide, even though the prescription was authorized under S.T.E.P.S.[®].³⁶

Such actions would cause a myriad of problems and significantly reduce Celgene's ability to effectively administer S.T.E.P.S.[®] and ensure patient safety. For example, Celgene would lose control over the inventory record. It would no longer be able to determine that the volume of drug dispensed matched the authorized prescriptions. Dispensing Thalomid[®] is the result of a complex cascade of events. Disrupting those events, as with generic substitution, creates a substantial safety risk. As FDA noted with respect to the initial isotretinoin programs, "[l]imiting the risk management program for each isotretinoin product strictly to that particular product would not be practical in a marketplace where substitution can occur freely."³⁷

(c) The Complexity and Cost of Appropriately Duplicating S.T.E.P.S.[®] Increases Potential Risks

There is also a serious question as to whether Barr or another generic manufacturer could safely and effectively implement its own risk management program equivalent to S.T.E.P.S.[®].

³⁶ Celgene notes that, if FDA were to approve a generic thalidomide product, Celgene would not be responsible for the risk management or drug product of the generic manufacturer. Adverse events resulting from those generic products could not be imputed to Celgene because S.T.E.P.S.[®] is intended to provide the safe distribution of Thalomid[®] only, and not any other product.

³⁷ Letter from J. Woodcock, M.D., CDER Director, to E. Flannery, Esq., Covington & Burling, Docket No. 2002P-0059 (November 8, 2002) at 3.

The S.T.E.P.S.[®] program is the result of intensive research and devoted effort by Celgene. S.T.E.P.S.[®] is administered under cGMP conditions. Unlike bioequivalence and other requirements for generic applications, there are no quantitative methods to evaluate or validate a generic's program against S.T.E.P.S.[®].³⁸

By way of example, the customer care group in S.T.E.P.S.[®] is divided into ten subgroups (e.g., risk management compliance, training, etc.). It includes ten dedicated risk intervention staff. Would Barr's program be equivalent to S.T.E.P.S.[®] if its customer care group were divided into six groups and had eight dedicated risk intervention staff instead of ten? It is the interaction of each specific component that makes S.T.E.P.S.[®] successful. Altering those components increases the related risks that the resulting system will not be as effective. In fact, as provided in the approval letter for Thalomid[®], Celgene is prohibited from changing the S.T.E.P.S.[®] program without a prior approval NDA supplement.

Even if Barr or another generic applicant were to duplicate the S.T.E.P.S.[®] program, it is unclear as to whether it would have the capacity and resources to implement the program. More than 175 Celgene employees work to implement S.T.E.P.S.[®] including over 50 employees solely dedicated to staffing the S.T.E.P.S.[®] service center. Would Barr or another generic company be able to dedicate and support an equivalent number of risk management personnel, particularly when the generic product would be indicated only for ENL? For example, it is unclear whether Barr would dedicate the necessary resources to educate, train, and monitor approximately 36,000 retail pharmacies for only about 50 ENL patients.³⁹ As detailed below, Celgene believes that Barr's apparent willingness to undertake the costly procedures required to safely distribute thalidomide in light of the very small number of ENL patients indicates that Barr is actually seeking approval to distribute its product for multiple myeloma.

³⁸ FDA may not rely on the non-public information contained in the Thalomid[®] application regarding S.T.E.P.S.[®] to help a generic applicant create its own program. Rather, FDA is authorized to rely only on the finding of safety and efficacy for Thalomid[®]. See Letter from J. Woodcock, M.D., CDER Director, to K. Sanzo, Esq., Morgan, Lewis & Bockius, LLP, Docket Nos. 2001P-0323, 2002P-0447, and 2003P-0408 (October 14, 2003) at 15 ("Reliance on FDA's conclusion that an approved drug is safe and effective does not involve disclosure to the ANDA or 505(b)(2) applicant - or to the public - of the data in the listed drug's NDA.").

³⁹ The majority of ENL patients receive thalidomide from academic centers or from their doctors through Celgene's Patient Assistance Program.

The specialized resources acquired by Celgene during its research and development cannot be underestimated. For example, the initial risk management plans implemented by the isotretinoin manufacturers were described as “equivalent and substitutable.”⁴⁰ However, the implementation by different manufacturers produced significantly different results. In particular, one manufacturer (*i.e.*, Bertek Pharmaceuticals) reported 18 pregnancies, while another manufacturer (*i.e.*, Ranbaxy Pharmaceuticals, Inc.) reported no pregnancies.⁴¹

Risk management programs as detailed and complex as S.T.E.P.S.[®] are relatively new. As described by FDA, “We’re just beginning along this road. And we have some tools that have been started to be employed in a lot of these programs, but are they doing what we really want them to do? And how . . . we test that is still a big question for us.”⁴² The degree of oversight provided by S.T.E.P.S.[®] is unprecedented.

(d) The Isotretinoin Situation Demonstrates that Risk Management Issues Create Very Real Safety Issues

Further, it is clear that the implementation of risk management plans create a very real safety concern. Although recent assessments indicate that there have been improvements in the isotretinoin restricted distribution program (iPLEDGE[™]), there were 122 pregnancies under iPLEDGE[™] in just its first year.⁴³ Such a situation should not be allowed to occur with respect to thalidomide. Furthermore, the CDER Ombudsman’s Office reported that the most frequent complaint it received in 2006 concerned the implementation of iPLEDGE[™]. According to the American Academy of Dermatology, “[p]atient care and safety are being compromised, the very

⁴⁰ Food and Drug Administration Drug Safety and Risk Management Advisory Committee in Joint Session with the Dermatologic and Ophthalmic Drugs Advisory Committee, February 26, 2004, Testimony of F. Sisto, Vice President of Regulatory Affairs for Mylan Labs. (on behalf of the generic isotretinoin manufacturers) at 142-3 (“[A]ll of these [isotretinoin] risk management programs are equivalent and substitutable or interchangeable and they are equivalent to the S.M.A.R.T. risk management program that was approved by FDA and implemented by Hoffman-La Roche in early 2002.”) (available at www.fda.gov/ohrms/dockets/ac/cder04.html#Dermatologic).

⁴¹ *Id.* at 146.

⁴² “FDA Putting System in Place for RiskMAP Evaluation and Management,” *The Pink Sheet*, Vol. 69, No. 27 at 13 (July 2, 2007) (Tab 7).

⁴³ “Briefing Document for iPLEDGE Year One Update,” Drug Safety and Risk Management Advisory Committee and the Dermatologic and Ophthalmic Drugs Advisory Committee, Barr Labs. et al. (released July 30, 2007) (available at <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4311b1-02-ipledge.pdf>).

things that the [iPLEDGE] program is designed to prevent.”⁴⁴ Patients are circumventing the risk management program and obtaining isotretinoin over the internet where there are no safety controls. As described in one article, “[w]eb sales of the drug [isotretinoin] are illegal, but the Food and Drug Administration acknowledges that some have turned to the Internet to skirt a federal program designed to control access to it.”⁴⁵ In response, FDA has even launched a website to warn consumers about the dangers of buying isotretinoin from the internet.⁴⁶ This could also occur with thalidomide, just as patients were obtaining the drug from unregulated buyers’ clubs before Celgene received marketing approval. Furthermore, these risks would be increased with thalidomide because iPLEDGE™ is a single program that coordinates information for all isotretinoin companies; whereas thalidomide would have multiple programs.

As evidenced by the difference in pregnancy exposures between one year of S.M.A.R.T.® or iPLEDGE™ compared to nine years of S.T.E.P.S.®, it is not always clear what makes a risk management program successful.⁴⁷ However, what is clear is that Celgene’s distribution of Thalomid® under S.T.E.P.S.® is effective. Although seemingly an administrative task, the implementation of such a tightly controlled plan is as important to the safety of the drug as any other approval requirement. The fact that a generic applicant would have to develop and implement its own thalidomide risk management plan equivalent to S.T.E.P.S.® raises serious safety risks. It is respectfully submitted that thalidomide is not the appropriate drug for FDA to take such risks, particularly when FDA is not, as in the isotretinoin case, already grappling with

⁴⁴ Food and Drug Administration Drug Safety and Risk Management Advisory Committee, February 10, 2006, Testimony of D. Thiboutot, M.D., American Academy of Dermatology, at 21-22 (emphasis added) (transcript available at <http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4202t2.pdf>); see also “Accutane iPLEDGE Glitches Warrant Start Up Delay, Dermatology Group Urges,” The Pink Sheet, Vol. 68, No. 8 at 14 (February 20, 2006) (“AAD said that the numerous flaws in the program could impact patient safety.”) (Tab 8).

⁴⁵ “FDA Tries to Thwart Online Accutane Sales,” The Wall Street Journal (March 29, 2007) (available at http://online.wsj.com/article_print/SB117512132133752405.html) (Tab 9).

⁴⁶ FDA WARNING: Risks of buying Accutane (isotretinoin) over the Internet (available at www.fda.gov/buyonline/accutane/).

⁴⁷ In addition to the 122 pregnancies reported during the first year of iPLEDGE™, FDA estimates that there were 120 fetal exposures to isotretinoin during the first year of the isotretinoin risk management plan used before iPLEDGE™, which was named S.M.A.R.T.®. Out of the estimated 120 fetal exposures, there were seven live births including two abnormal babies. Food and Drug Administration Drug Safety and Risk Management Advisory Committee in Joint Session with the Dermatologic and Ophthalmic Drugs Advisory Committee, February 26, 2004, Slide Presentation by M. Pitts and A. Brinker, FDA’s Office of Drug Safety.

an existing public health issue contributed to by multiple manufacturers marketing the same drug under parallel risk management plans.

(e) It is Unreasonable to Expect Celgene to Participate in a Joint Risk Management Program

Celgene acknowledges that Hoffman-LaRoche Inc. and the generic isotretinoin manufacturers jointly implemented iPLEDGE™. However, the isotretinoin situation is very different from the thalidomide situation, and, for a variety of reasons, Celgene should not be expected to share responsibility for administration of a risk management plan like S.T.E.P.S.® with Barr. Unlike the isotretinoin situation, Celgene has orphan drug exclusivity and, as discussed below, believes that Barr is expecting to market its generic thalidomide product in violation of Celgene's exclusivity. It would be patently unreasonable for FDA to expect Celgene to facilitate the violation of its own orphan drug exclusivity by joining with Barr in a risk management plan, where the lion's share of the responsibility would inevitably fall to Celgene. Furthermore, in contrast to the isotretinoin situation, Celgene has patents directed to the S.T.E.P.S.® program. Celgene does not believe that FDA has either the authority or the right to expect Celgene to share its patented technology or business methods with a company that seeks to directly compete with one of Celgene's primary products, particularly as Celgene markets a limited number of products.⁴⁸ Celgene firmly believes that its patents directed to the S.T.E.P.S.® program preclude Barr's proposed plan. Barr has contested the validity of Celgene's patents, and the parties are currently litigating the issues. Also, the joint iPLEDGE™ program was implemented to address significant issues resulting from the fact that multiple manufacturers were *already* marketing the same drug under parallel risk management plans – the very issue approving Barr's ANDA would create for thalidomide.

⁴⁸ In addition to Thalomid®, Celgene markets only Revlimid® (lenalidomide) and Alkeran® (melphalan) (manufactured and packaged by GlaxoSmithKline).

**3. A Generic Thalidomide Products Raises Unacceptable Safety Risks
Because Its Labeling Must Exclude Information Protected by Exclusivity**

Generally, a generic thalidomide product must have the same labeling as Thalomid[®].⁴⁹ The statute authorizes the labeling for an ANDA product to differ from the labeling for the reference product only when the differences are due to a suitability petition or to the fact that the ANDA product and the reference product are produced or distributed by different manufacturers.⁵⁰ FDA's regulations seek to broaden that authority somewhat. They provide that the labeling for an ANDA product may differ from the labeling for the reference product when "aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."⁵¹ When the labeling omission renders the generic product less safe than the reference product for the remaining, non-protected indication, then FDA may not approve the ANDA.⁵² As detailed below, the labeling omission for generic thalidomide would render the generic product less safe than Thalomid[®] for the remaining, non-protected ENL indication. Accordingly, FDA may not approve a generic thalidomide product for ENL. Even if the labeling carve-out did not make the generic less safe than Thalomid[®] for the ENL indication, the labeling omission would raise significant overall safety and misbranding concerns for the generic product.

**(a) The Labeling Carve-Out Would Render a Generic Thalidomide
Product Less Safe than Thalomid[®] for the Remaining,
Unprotected ENL Indication**

The labeling for Thalomid[®] includes two indications, ENL and multiple myeloma. The multiple myeloma indication, however, is protected by orphan drug exclusivity until 2013. Consequently, until 2013, neither Barr nor any other generic manufacturer may seek approval for

⁴⁹ 21 U.S.C. § 355(j)(2)(A)(v).

⁵⁰ *Id.*

⁵¹ 21 C.F.R. § 314.127(a)(7); *see also Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996) (upholding FDA's determination that 21 U.S.C. § 355(j)(2)(A)(v) allows an ANDA applicant to carve-out a protected indication).

⁵² 21 C.F.R. § 314.127(a)(7).

the multiple myeloma indication. Rather, a generic company can at this point seek approval only for the ENL indication and must “carve out” the sections of the Thalomid[®] labeling related to the multiple myeloma indication. However, labeling with the omitted information would render the generic drug product less safe than Thalomid[®]. This is so even for the remaining ENL indication. Barr’s application is thus unapprovable pursuant to FDA’s regulations.

Thalomid[®] was initially approved in 1998 for the treatment ENL, which is an inflammatory complication of leprosy that results in painful skin lesions. The labeling provides that Thalomid[®] is administered daily at a dose of 100 to 300 mg/day to treat ENL. Dosing is continued until the symptoms have subsided. At that point, patients are tapered off Thalomid[®] in 50 mg decrements every two to four weeks. Additionally, the labeling provides that corticosteroids may be used concomitantly with Thalomid[®] for the treatment of ENL, specifically in patients with moderate to severe neuritis associated with severe ENL.

In 2006, Thalomid[®] was approved for the treatment of multiple myeloma. As part of the multiple myeloma approval, Celgene significantly changed Thalomid[®]’s labeling. The new labeling added indication and dosing information for multiple myeloma. Thalomid[®] is administered in combination with dexamethasone, which is a corticosteroid, in 28-day treatment cycles to treat multiple myeloma. The dose of Thalomid[®] is 200 mg administered daily. The dose of dexamethasone is 40 mg administered on days 1-4, 9-12, and 17-20 every 28 days.

In addition to indication and dosing information, Celgene strengthened the labeling information regarding thrombotic events, such as deep venous thrombosis and pulmonary embolus. The old labeling (*i.e.*, the labeling when Thalomid[®] was indicated only for ENL) warned that thrombotic events have been reported in patients treated with Thalomid[®], but that “[i]t is not known if concomitant therapy with other medications including anticancer agents, are a contributing factor.”⁵³ In contrast, the new labeling (*i.e.*, the labeling approved with the multiple myeloma indication) deleted the old labeling language. It now makes clear that other medications do indeed increase the risk of thromboembolic events. Specifically, Celgene added

⁵³ Thalomid[®] package insert approved on October 27, 2003 at 6 (Thrombotic Events) (available at http://www.fda.gov/cder/foi/label/2003/20785slr022,023,024_thalomid_lbl.pdf).

a black box warning detailing the increased risk of venous thromboembolic events from the use of Thalomid[®] in multiple myeloma patients “when thalidomide is used in combination with standard chemotherapeutic agents including dexamethasone.”⁵⁴

The new labeling regarding the combination use of thalidomide with chemotherapeutic agents, such as dexamethasone, has safety implications for the treatment of ENL as well. Similar to multiple myeloma, ENL may be treated with a combination of thalidomide and chemotherapeutic agents, including dexamethasone and prednisolone. In fact, dexamethasone and prednisolone are corticosteroids, and the labeling for Thalomid[®] specifically provides that corticosteroids may be used concomitantly with thalidomide to treat ENL in certain situations. Like multiple myeloma patients, ENL patients taking thalidomide in combination with a chemotherapeutic agent are also at risk for thromboembolic events. As one clinician warned in a publication describing a case of deep vein thrombosis in an ENL patient who was treated with thalidomide, prednisolone, and dexamethasone-cyclophosphamide, “clinicians need to be vigilant about potential occurrence of thrombotic complications in these [ENL] patients especially when glucocorticoids or other chemotherapeutic agents are being used concomitantly.”⁵⁵ A generic thalidomide product having labeling that omitted the information regarding the use of thalidomide in combination with dexamethasone and other chemotherapeutic agents would be less safe than Thalomid[®] for the remaining, non-protected ENL indication.

Furthermore, the new labeling explains the signs and symptoms of a thromboembolic event. More importantly, it provides instructions on decreasing such risks. For example, the new labeling states that appropriate candidates may benefit from concurrent prophylactic anticoagulation or aspirin treatment. Without such labeling information, a generic thalidomide product would be less safe than Thalomid[®] for the ENL indication.

⁵⁴ Thalomid[®] package insert approved on May 25, 2006 at 4 (Venous Thromboembolic Events) (available at <http://www.fda.gov/cder/foi/label/2006/021430s000,020785s0311bl.pdf>).

⁵⁵ Sharma, NL et al., “Deep Vein Thrombosis: A Rare Complication of Thalidomide Therapy in Recurrent Erythema Nodosum Leprosum,” *Int. J. Lepr. Other Mycobact. Dis.* 72(4):483-5, 485 (Dec. 2004) (Tab 10).

In addition, the new labeling added a section titled “Adverse Events in Multiple Myeloma Controlled Clinical Trial.” This section describes the types and frequency of adverse events associated with the use of Thalomid[®] and dexamethasone in multiple myeloma patients, and includes a table showing the severity of such events. The adverse events described in the new labeling include sensory neuropathy, confusion, hypocalcemia, edema, constipation, dyspnea, rash/desquamation, and thrombosis/embolism. This information is important to the safety of patients taking both thalidomide and dexamethasone. As ENL patients may be treated with both thalidomide and dexamethasone, the new labeling information regarding adverse events is also relevant to ENL. Omitting such adverse event information from the labeling would make a generic thalidomide product less safe than Thalomid[®] for the remaining ENL indication.

Although some of Celgene’s new labeling involves risk information, Celgene does not believe that FDA may disregard Celgene’s exclusivity and allow a generic’s labeling to include such information.⁵⁶ In particular, FDA’s regulations provide that FDA should refuse to approve a generic product when protected labeling makes the generic product less safe than the reference product and not simply authorize the generic product to include the protected labeling.

(b) A Generic Thalidomide Product with the Omitted Multiple Myeloma Labeling Raises Overall Safety and Misbranding Issues

In addition to making a generic product less safe than Thalomid[®] with respect to ENL, the labeling carve-out also raises overall safety and misbranding issues. Specifically, a generic thalidomide product labeled only for ENL would be properly labeled for approximately one half of 1% (0.5%) of all users of thalidomide, and not labeled for the rest of the patients. Such a situation would raise significant safety concerns that cannot be ignored.

Despite the omission of multiple myeloma information from the labeling, state requirements regarding generic substitution and off-label use mean that the generic thalidomide

⁵⁶ For example, the statutory provision governing three-year exclusivity for an NDA supplement containing new clinical studies, except bioavailability studies, provides that FDA may not approve an ANDA for the “change approved in the supplement.” 21 U.S.C. § 355(j)(5)(F)(iv). There is nothing in the statute that indicates that exclusivity is available for all changes, except those changes related to risk information. Furthermore, the statute specifically excludes from exclusivity information generated from bioavailability studies. This certainly suggests that Congress could also have excluded risk information if that had been its intent.

product would likely be dispensed for the treatment of multiple myeloma.⁵⁷ Dispensing a generic thalidomide product to multiple myeloma patients with the omitted multiple myeloma labeling information would greatly increase the safety risks for the product.⁵⁸ In particular, the generic's labeling would presumably not include the black box warning regarding the risks of thromboembolic events. Nor could it include the description of adverse events related to the treatment of multiple myeloma. Additionally, the labeling for the generic product could not include the description of a clinical study in multiple myeloma patients, which was added to the labeling as part of the multiple myeloma approval. The description sets forth the efficacy of Thalomid[®] and dexamethasone versus dexamethasone alone, including several tables regarding baseline patient demographics and disease characteristics. Furthermore, the generic's labeling could not include the relevant dosage and administration information. Multiple myeloma is treated with thalidomide in combination with dexamethasone on a complex pulsing schedule. Specifically, dexamethasone is administered on days 1-4, 9-12, and 17-20 every 28 days.

Without the information described above, the risks associated with the use of generic thalidomide, including dosing mistakes and other medication errors, related to thalidomide's primary use as a treatment for multiple myeloma would greatly increase. According to the National Academy of Sciences, "The probability of medication dosing errors is greatly increased with high-risk medications that have complex dosing regimens, such as oral chemotherapy agents"⁵⁹ Medical errors may be responsible for as many as 98,000 deaths annually in the United States.⁶⁰ Furthermore, it has been estimated that 41% of fatal medical errors are due to an

⁵⁷ Issues raised by the effect of generic substitution on the implementation of Barr's risk management program are discussed elsewhere in this petition.

⁵⁸ The public health benefits of complete and accurate labeling are underscored by FDA's DailyMed initiative, through which FDA and the National Library of Medicine are making the content of labeling electronically available to consumers, pharmacists, and healthcare prescribers. As recognized by FDA, "[t]o maximize its ability to serve as a useful resource to consumers, pharmacists, and healthcare providers, DailyMed must contain the most up-to-date and comprehensive drug information available." FDA Draft Guidance for Industry: Public Availability of Labeling Changes in "Changes Being Effectuated" Supplements (September 2006) at 2.

⁵⁹ "Preventing Medication Errors," Committee on Identifying and Preventing Medication Errors, Institute of Medicine, National Academy of Sciences (July 2006) at 83.

⁶⁰ See "Physician Labeling Proposal," HHS News (December 21, 2000) (available at <http://www.fda.gov/bbs/topics/NEWS/NEW00745.html>).

improper dose, and that 44% of errors are caused by knowledge and performance deficits.⁶¹ Celgene does not dispute FDA's authority to approve a generic for less than all of the reference product's indications or with omitted labeling language. However, Celgene believes that the unique circumstances surrounding thalidomide raise overall safety concerns that must not be disregarded.

Additionally, although the statute authorizes FDA to approve in certain circumstances a generic with labeling that differs from the reference product, it surely does not require the approval of such generics in every situation. In particular, the labeling for the generic still must comply with other statutory requirements, including the prohibition against misbranding. A drug is misbranded if its labeling is false or misleading.⁶² The statute provides that labeling is misleading when it:

fails to reveal facts . . . material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising or under such conditions of use as are *customary or usual*.⁶³

FDA has previously addressed the intersection of misbranding requirements to labeling carve-out situations in terms of the intended use of the generic product.⁶⁴ FDA's regulations define "intended use" to mean "the objective intent of the persons legally responsible for the labeling of drugs."⁶⁵ To determine objective intent, FDA has typically looked at the proposed indication for the generic product. Consequently, there have been no determinations that the carved-out labeling resulted in a misbranded product when the product was properly labeled for the proposed indication.

⁶¹ Wharton, A., "CE: Oh No! Not Another Medication Error!," Drug Topics (November 22, 2004) at 2 (Tab 11).

⁶² 21 U.S.C. § 352(a).

⁶³ 21 U.S.C. § 321(n) (emphasis added).

⁶⁴ See, e.g., Docket No. 2003P-0321 (providing that an ANDA applicant may limit the intended use of its product as evidenced in its proposed labeling).

⁶⁵ 21 C.F.R. § 201.128.

However, FDA must look beyond the intended use of the product to the “customary or usual” use of the product. As described above, the statute requires labeling to contain facts that are material to a product’s customary or usual use.⁶⁶ The customary or usual use of a product is not dependent on the objective intent of the ANDA applicant, as evidenced by the proposed indication. Rather, a drug product’s customary or usual use is based on how a product is routinely used in practice. Thalidomide’s overwhelmingly common use is the treatment of multiple myeloma. Thus, without the labeling information for multiple myeloma, Celgene believes that Barr’s product, and other generic thalidomide products, would be misbranded.

Accordingly, FDA should not approve Barr’s ANDA or any other application for a generic thalidomide product indicated for ENL because a carve-out of all multiple myeloma information would make the product unsafe for the most likely recipients - the multiple myeloma patients. At the same time, it would be inappropriate to include the information necessary to make the generic label adequate for the safe use of the product by patients most likely to receive it, because that indication (multiple myeloma) is protected by orphan drug exclusivity.

4. A Generic Thalidomide Product Provides Virtually No Benefit

As detailed above, an application for a generic thalidomide product raises serious questions of safety. Yet, a generic thalidomide product provides few, if any, benefits. In light of Celgene’s orphan drug exclusivity, the proposed indication for a generic thalidomide product could only be ENL, and would only legally serve approximately 50 patients. There are just over 100 ENL patients on Thalomid[®] in the United States. Approximately half of those patients receive Thalomid[®] for free from Celgene through Celgene’s needs-based Patient Assistance Program. Thus, any properly labeled and marketed generic thalidomide would benefit an exceedingly small patient population that already has other therapeutic options.

Importantly, the World Health Organization (“WHO”), which initially recommended thalidomide to treat ENL, has now reversed its position and does not believe that thalidomide should be approved globally for the treatment of ENL. As stated by the WHO, “For the reason

⁶⁶ 21 U.S.C. § 321(n).

of well-known teratogenic side effects, WHO does not support use of thalidomide for the management of ENL in leprosy.”⁶⁷ In particular, the WHO notes that thalidomide has a limited ability to control neuritis associated with ENL, which is the major cause of permanent disabilities in leprosy, and a high relapse rate. Accordingly, the WHO recommends a multidrug therapy that includes clofazimine and prednisolone. Clofazimine is described as the drug of choice for the management of chronic, recurrent ENL reactions, because it has both anti-reaction and anti-leprosy effects, while prednisolone is described as the drug of choice for those patients suffering from ENL associated with neuritis.⁶⁸ Thus, the clinical benefits of Barr’s ANDA for the use of thalidomide to treat ENL are not significant compared with other therapeutic options. Even looking beyond a generic’s proposed indication, though, any benefits received from a generic thalidomide product simply do not seem to begin to outweigh the associated risks.

B. The Approval of A Generic Thalidomide Product Would Violate Celgene’s Orphan Drug Exclusivity

The Orphan Drug Act of 1983 provides incentives for the development of drugs to treat rare diseases that affect only a small patient population. A product is designated as an orphan drug when it is used to treat a disease that affects fewer than 200,000 people or when there is no reasonable expectation that the cost of developing and making the drug available in the United States will be recovered by the company. Among other incentives, the Orphan Drug Act provides seven years of exclusivity for orphan drug products. Without such incentives, there is a substantial likelihood that such diseases, which are often fatal, would be left untreated. As evidence of the importance of orphan drug exclusivity, Congress provided an exclusivity period of seven years, which is the longest period of exclusivity available for a drug product. Specifically, the statute provides that FDA may not approve another application “for such drug

⁶⁷ WHO Guidelines for Management of Severe *Erythema Nodosum Leprosum* (ENL) Reaction (available at <http://www.paho.org/English/AD/DPC/CD/who-enl-guidelines.htm>) (Tab 12) at 2.

⁶⁸ “No Role for Thalidomide in Leprosy,” WHO Leprosy Team, World Health Organization (May 12, 2003) (available at <http://www.paho.org/English/AD/DPC/CD/thalidomide.htm>) (Tab 1) (stating that “leprosy does not need thalidomide”).

for such disease or condition . . . until the expiration of seven years from the date of the approval of the approved [orphan drug product] application.”⁶⁹

FDA has interpreted the statute to mean that “FDA will not approve another sponsor’s marketing application *for the same drug* before the expiration of 7 years from the date of such approval . . . ”⁷⁰ With respect to small molecules, FDA has defined the term “the same drug” to mean “a drug that contains the same active moiety as a previously approved drug and is *intended for the same use* as the previously approved drug . . . ”⁷¹ FDA’s regulations define “intended use” to mean “the objective intent of the persons legally responsible for the labeling of drugs.”⁷²

1. The Present Case is Different from *Sigma Tau Pharms. Inc. v. Schwetz*

Typically, FDA determines the proposed use of a generic product by reviewing the labeling in the application, particularly the proposed indication. For example, in *Sigma Tau Pharms. Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002), the court upheld FDA’s decision to approve an ANDA for the proposed indication even though the reference product had a second indication that was protected by orphan drug exclusivity. In that case, Sigma Tau had argued that evidence in addition to the generic’s proposed labeled use demonstrated that the generic product would be used in violation of Sigma Tau’s orphan drug exclusivity. For example, Sigma Tau noted that the 80% of the market for the drug was for the protected indication and that the Centers for Medicare and Medicaid Services do not distinguish between orphan and generic drugs in making payments. The court rejected Sigma Tau’s arguments and agreed with FDA’s decision to rely on the generic’s proposed labeling.⁷³

The thalidomide situation is different from *Sigma Tau*. Importantly, the *Sigma Tau* case did not involve the significant safety issues that are before the FDA with respect to generic thalidomide, which by themselves should prevent the approval of generic thalidomide. As

⁶⁹ 21 U.S.C. § 360cc(a).

⁷⁰ 21 C.F.R. § 316.31(a) (emphasis added); *see also id.* § 316.3(12) (defining orphan drug exclusive approval).

⁷¹ *Id.* § 316.3(b)(13).

⁷² *Id.* § 201.128.

⁷³ *Sigma Tau*, 288 F.3d at 145.

detailed above, generic thalidomide raises important safety issues regarding risk management and labeling. Additionally, *Sigma Tau* did not involve a risk management system that requires the generic company to be actively involved in the distribution of the generic product in violation of the orphan drug exclusivity.

2. The Evidence Shows that Barr is Seeking Approval to Market Its Product in Total Disregard for Celgene's Orphan Drug Exclusivity

Unlike the generic company in *Sigma Tau*, Barr's proposed labeling indicates that Barr is seeking approval to distribute generic thalidomide for more than just the proposed ENL indication. Barr's proposed ENL indication must be analyzed in light of the other conditions of use contained in the application. In particular, Celgene does not believe that Barr's limited indication is consistent with Barr's restricted distribution material, which presumably does not exclude multiple myeloma. Without completely excluding multiple myeloma from its conditions of use, Barr is essentially seeking approval to distribute generic thalidomide beyond the ENL patient population in violation of Celgene's orphan drug exclusivity.

Similar to Thalomid[®], Celgene presumes that Barr's restricted distribution program will require the active participation of Barr to authorize each prescription. For example, Barr would have to actively consult with and register prescribers and patients. Additionally, Barr would have to collect detailed information regarding each patient and prescriber to determine whether a prescription may be dispensed. Importantly, Barr also would need to issue authorization and confirmation numbers for each prescription. Therefore, unlike the typical generic situation, Barr would have direct control over who receives its generic thalidomide product through its restricted distribution program.

Unless specifically restricted to exclude multiple myeloma patients, Barr's distribution program would thus seem to be wholly inconsistent with Celgene's orphan drug exclusivity. However, as far as Celgene is aware, Barr has not limited its restricted distribution program to prohibit the authorization of prescriptions for multiple myeloma patients. Furthermore, Celgene does not believe that Barr has indicated that it will exclude multiple myeloma patients and oncologists. The scope of Barr's restricted distribution plan is a condition of use similar to the proposed indication. In fact, the restricted distribution plan is probably more important than the

proposed indication in determining the labeled use because the plan actually limits the types of prescriptions that Barr may authorize. As FDA noted in Thalomid[®]'s approval letter, the restricted distribution plan is an "integral part of the approved NDA for this product and is an essential component of the terms of this NDA's approval by FDA for marketing this product."

Furthermore, the implementation and management of S.T.E.P.S.[®] is very costly. The fact that Barr is apparently willing to undertake such a resource intensive program despite the miniscule number of ENL patients who may purchase the drug suggests that Barr intends to distribute its product for multiple myeloma in violation of Celgene's orphan drug exclusivity. Indeed, a recent presentation by Barr to its investors actually indicates that Barr is seeking approval to market its generic product without regard for Celgene's orphan drug exclusivity. In July 2007, Barr presented a slide to investors titled "Disclosed Patent Challenges." On that slide, Barr listed Thalomid[®] as a market opportunity, and represented that it had sales of \$398 million.⁷⁴ The sales number presented by Barr to its investors includes the protected multiple myeloma market. Importantly, Barr's slide makes no mention of Celgene's orphan drug exclusivity for multiple myeloma. Nor does it mention the fact that Barr is prohibited from marketing its product for that indication. It is clear that Barr intends the marketing and use of its product to completely disregard Celgene's orphan drug exclusivity. The FDA should not be a party to such an evasion of the statute.

In determining whether to approve a generic product, FDA must balance the equities between protecting orphan drug exclusivity and making generic products available to the public.⁷⁵ In addition to the safety and risk management issues presented with respect to generic thalidomide (but not faced by FDA or the court in *Sigma Tau*), the proposed indication for generic thalidomide (*i.e.*, ENL) is a miniscule fraction of the market. Celgene provides free thalidomide to approximately half of the ENL patients. Therefore, it is respectfully submitted that the totality of the circumstances where FDA is being asked to approve an additional

⁷⁴ Barr Pharmaceuticals, Inc., Generic and Proprietary Pharmaceuticals, Investor Presentation July 2007 (available at <http://phx.corporate-ir.net/phoenix.zhtml?c=60908&p=irol-presentations>) (slide attached at Tab 2).

⁷⁵*Sigma Tau*, 288 F.3d at 148.

manufacturer of thalidomide for ENL dictate that the orphan drug exclusivity should be preserved and that such preservation does not run afoul of *Sigma Tau*.

3. At a Minimum, the Restricted Distribution Program of any Generic Thalidomide Product Should Exclude Multiple Myeloma

The significant safety concerns, coupled with Barr's disregard for Thalomid[®]'s orphan drug exclusivity for multiple myeloma, means that FDA should not approve its ANDA at all. However, if FDA were to decide to approve Barr's ANDA, or any other application for generic thalidomide, FDA should, at a minimum, ensure that the conditions of use contained in the application are consistent with Celgene's orphan drug exclusivity. Otherwise, FDA would be expanding the generic product's limited ENL indication and granting approval to dispense generic thalidomide in violation of Celgene's orphan drug exclusivity. Accordingly, under these unique circumstances, FDA should ensure that the generic thalidomide product is not marketed or distributed to multiple myeloma patients.

Typically, when the FDA approves a generic product, the generic manufacturer markets the product for the indication for which exclusivity has lapsed and has no control over whether third parties dispense the product for other uses, including those protected by exclusivity. In contrast, Barr and other generics will have complete control over who receives generic thalidomide, and for what purpose they receive it. The risk management plan for thalidomide requires the generic manufacturer to be actively involved in approving prescriptions. It would be an easy matter for the system to limit the distribution of a generic thalidomide product to ENL patients, as the nature of the restricted distribution program is to track detailed information about each prescription and prevent distribution in inappropriate circumstances. For example, the registration surveys required of patients and doctors could easily capture whether the patient required treatment for ENL. Barr and other generics should be allowed to issue prescription authorization numbers only for ENL patients and not for patients with multiple myeloma.

As noted in *Sigma Tau*, FDA must balance the goals of the Orphan Drug Act (e.g., promoting the development of drugs for rare diseases through incentives such as exclusivity)

with the goals of the Hatch-Waxman Act (*e.g.*, providing safe and effective generic drugs).⁷⁶ Allowing Barr to actively dispense thalidomide for the treatment of multiple myeloma through its restricted distribution program would completely vitiate Celgene's orphan drug exclusivity. On the other hand, prohibiting Barr from registering multiple myeloma patients and authorizing prescriptions for multiple myeloma would significantly protect Celgene's exclusivity without detriment to the Hatch-Waxman Act. As the multiple myeloma indication is protected by exclusivity, Barr and other generics have no legitimate interest in actively registering multiple myeloma patients or authorizing such prescriptions. For FDA to grant Celgene orphan drug exclusivity for multiple myeloma while facilitating the active authorization of prescriptions for multiple myeloma in violation of Celgene's exclusivity would be an unlawful application of the statutory scheme.

Furthermore, FDA will be in a position to closely monitor Barr and other generics to determine whether they are actively dispensing its generic thalidomide product in violation of Celgene's orphan drug exclusivity. As with the S.T.E.P.S.[®] program, the generic's restricted distribution program, including the records, will be subject to FDA inspection. As such, to the extent that FDA learns that Barr or another generic manufacturer is violating Celgene's orphan drug exclusivity by registering multiple myeloma patients and authorizing prescriptions for multiple myeloma, FDA may require corrective action.

C. Conclusion

Due to its teratogenicity, thalidomide was responsible for thousands of malformed babies in the 1960s and was the genesis for an overhaul to the U.S. drug approval laws. Despite the stigmas associated with thalidomide, Celgene took the legal, scientific, and financial risks involved to bring an approved thalidomide product to market. In particular, Celgene developed and implemented an unprecedented restricted distribution program, S.T.E.P.S.[®], to prevent fetal exposure to Thalomid[®].

The FDA must now consider approval for a generic thalidomide product for ENL. Due to unacceptable safety risks associated with generic thalidomide, FDA should refrain from

⁷⁶ *Id.*

approving Barr's ANDA and any other application for a generic thalidomide product. FDA has indicated that an ANDA should not be approved when there is a reasonable basis to conclude that the ANDA raises serious questions of safety. Thalidomide is not the typical drug, and an application for generic thalidomide raises significant safety issues.

Importantly, Barr and other generic applicants will have to develop and implement a restricted distribution program equivalent to Celgene's S.T.E.P.S.[®] program. At a minimum, without such a program, thalidomide is simply not safe. However, multiple thalidomide risk management plans increase the risk of confusion and medication errors. The S.T.E.P.S.[®] program is a product-specific and closed distribution program. It is unclear how multiple programs could operate effectively, particularly in light of generic substitution.

Although seemingly an administrative issue, the operation of multiple risk management plans creates very real safety risks. Recent assessments may be indicating that there have been improvements in the isotretinoin restricted distribution program (iPLEDGE[™]). However, there were 122 pregnancies under iPLEDGE[™] in just its first year. The current levels of isotretinoin pregnancies underscore the risks associated with generic thalidomide. FDA should not take those risks with thalidomide, particularly as FDA is not, as with isotretinoin, already grappling with existing public health issues contributed to by multiple manufacturers marketing the same drug under parallel risk management plans.

Furthermore, a generic thalidomide product would be unsafe due to the omission of labeling information protected by exclusivity. The use of thalidomide to treat multiple myeloma is protected by Celgene's orphan drug exclusivity, which expires in 2013. Accordingly, Barr and other generic applicants may not seek approval for multiple myeloma and must carve-out the related labeling. Such information includes strengthened information regarding the risks of using thalidomide in combination with dexamethasone, as well as clinical trial data and complex dosing information.

A generic thalidomide product that omits the protected labeling would be less safe than Thalomid[®] for the remaining ENL indication because, similar to multiple myeloma patients, ENL patients may take Thalomid[®] in combination with dexamethasone. Additionally, a generic

product without the multiple myeloma information would create an overall safety risk and seem to be misbranded. Without the protected information, a generic thalidomide product would be properly labeled for approximately one half of 1% (0.5%) of prescriptions and not properly labeled for the rest of the population. Having a product labeled for such a small percentage of the patient population substantially increases the risks of otherwise preventable medication errors. Additionally, the omission seems contrary to the statutory requirement that labeling include material facts related to the customary or usual use of the product.

In addition to the safety risks, an application for generic thalidomide should not be approved because it would violate Celgene's orphan drug exclusivity. As a result of its efforts, Celgene earned orphan drug exclusivity for the use of thalidomide to treat multiple myeloma, which expires in 2013. Due to Celgene's orphan drug exclusivity, Barr's proposed indication can only be ENL, which represents a tiny fraction of Thalomid® prescriptions.

Barr's restricted distribution program material presumably would not exclude multiple myeloma. Accordingly, Barr may be actively registering multiple myeloma patients and oncologists, and issuing authorization and confirmation numbers for generic thalidomide to treat multiple myeloma. If Barr has not excluded multiple myeloma from all of its conditions of use, then FDA would be allowing Barr to authorize multiple myeloma prescriptions and distribute generic thalidomide in violation of Celgene's orphan drug exclusivity.

If FDA were to decide to approve Barr's application or any other application for generic thalidomide, then Celgene requests that FDA require the restricted distribution program for the generic product to exclude multiple myeloma. Prohibiting the generic company from registering multiple myeloma patients and authorizing multiple myeloma prescriptions would protect Celgene's orphan drug exclusivity without impacting the goals of the Hatch-Waxman Act.

C. ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusions under 21 C.F.R. § 25.31.

D. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted upon request of the Commissioner.

E. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



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