



October 17, 2000

Tel 908 598-7661
Fax 908 522-1781

Dockets Management Branch, FDA
12420 Parklawn Dr., Rm. 1-23
Rockville, MD 20857

Re: Docket 97P-0079; Comments on Citizen Petition

Dear Sir or Madame:

Novartis Consumer Health, Inc. ("NCH") submits these comments on the citizen petition filed March 3, 1997, by the law firm of Greenberg Traurig Hoffman Lipoff Rosen & Quentel (hereafter: "the Greenberg Petition") seeking to deny exclusivity to nicotine patch smoking cessation products for OTC use, including NCH's product, Habitrol®. For the reasons stated herein, FDA must deny the Greenberg Petition and grant exclusivity to Habitrol®.

I. BACKGROUND

On January 13, 1984, FDA approved the first prescription smoking cessation product containing nicotine, Nicorette®, a chewable gum developed by Merrell Dow, now a part of Hoechst Marion Roussel ("HMR"). Since Nicorette®'s introduction in 1984, FDA has approved several other prescription products, in various dosage forms, containing nicotine and indicated generally to help people quit smoking. In approving the prescription nicotine substitution products, FDA has consistently recognized that each innovator's product required its own full new drug application under § 505(b) of the Federal Food, Drug, and Cosmetic Act ("the Act"),¹ and, thus, was a distinctly different product from any other nicotine substitution drug product.²

In March 1994, FDA issued a draft guidance on how to demonstrate the safety and effectiveness of nicotine substitution products when used under OTC conditions. A copy of that draft guidance is attached to, and incorporated by reference into, these comments as Exhibit A. Compliance with that draft guidance required that the holders of prescription nicotine substitution products provide detailed safety and effectiveness data to FDA to support the OTC use of their products.

On February 9, 1996, the agency approved an application by SmithKline Beecham Consumer Healthcare ("SmithKline") to "switch" Nicorette® from sale solely as a prescription

¹ Codified at 21 U.S.C. § 321, *et seq.*

² FDA's handling of each company's nicotine substitution product under separate new drug applications – and the parallel agency conclusion that these various nicotine substitution products are legal distinct products – is consistent with the Supreme Court's holding in U.S. v. Generix Drug Corp., 460 U.S. 453 (1983).

97P-0079

C 2



October 17, 2000

Tel 908 598 7661
Fax 908 522 1781

Dockets Management Branch, FDA
12420 Parklawn Dr., Rm. 1-23
Rockville, MD 20857

Re: Docket 97P-0079; Comments on Citizen Petition

Dear Sir or Madame:

Novartis Consumer Health, Inc. ("NCH") submits these comments on the citizen petition filed March 3, 1997, by the law firm of Greenberg Traurig Hoffman Lipoff Rosen & Quentel (hereafter: "the Greenberg Petition") seeking to deny exclusivity to nicotine patch smoking cessation products for OTC use, including NCH's product, Habitrol®. For the reasons stated herein, FDA must deny the Greenberg Petition and grant exclusivity to Habitrol®.

I. BACKGROUND

On January 13, 1984, FDA approved the first prescription smoking cessation product containing nicotine, Nicorette®, a chewable gum developed by Merrell Dow, now a part of Hoechst Marion Roussel ("HMR"). Since Nicorette®'s introduction in 1984, FDA has approved several other prescription products, in various dosage forms, containing nicotine and indicated generally to help people quit smoking. In approving the prescription nicotine substitution products, FDA has consistently recognized that each innovator's product required its own full new drug application under § 505(b) of the Federal Food, Drug, and Cosmetic Act ("the Act"),¹ and, thus, was a distinctly different product from any other nicotine substitution drug product.²

In March 1994, FDA issued a draft guidance on how to demonstrate the safety and effectiveness of nicotine substitution products when used under OTC conditions. A copy of that draft guidance is attached to, and incorporated by reference into, these comments as Exhibit A. Compliance with that draft guidance required that the holders of prescription nicotine substitution products provide detailed safety and effectiveness data to FDA to support the OTC use of their products.

On February 9, 1996, the agency approved an application by SmithKline Beecham Consumer Healthcare ("SmithKline") to "switch" Nicorette® from sale solely as a prescription

¹ Codified at 21 U.S.C. § 321, *et seq.*

² FDA's handling of each company's nicotine substitution product under separate new drug applications – and the parallel agency conclusion that these various nicotine substitution products are legal distinct products – is consistent with the Supreme Court's holding in *U.S. v. Generix Drug Corp.*, 460 U.S. 453 (1983).

product to OTC marketing.³ In conjunction with that approval, FDA awarded SmithKline three years of exclusive marketing pursuant to the Drug Price Competition and Patent Term Restoration Act of 1984 (“the Waxman-Hatch Act”)⁴, as it amended the Act.

The issue of whether FDA could validly grant exclusivity to Nicorette® upon its approval for OTC marketing was the subject of a petition filed by the law firm of McKenna & Cuneo, L.L.P. (hereafter: “The Nicorette® Petition”). The Nicorette® Petition, filed in November 1995, even before the Nicorette® OTC approval, raised numerous objections to any potential grant of exclusivity to Nicorette® relating to its potential Rx-to-OTC switch. In February 1996, shortly after Nicorette®’s approval for OTC marketing, the McKenna firm filed a Petition to Stay any award of exclusivity to the Nicorette® Rx-to-OTC switch.

FDA denied both the Nicorette® Petition and the Petition to Stay by letter dated October 31, 1996, to Gary L. Yingling, Esq. (hereafter: “the Yingling Letter”). The Yingling Letter, in explaining FDA’s decision to award three-year exclusivity to the Nicorette® Rx-to-OTC switch applications,⁵ discusses many aspects of FDA’s views on the applicability of three-year exclusivity to Rx-to-OTC switches⁶ and, ultimately, determined that the Nicorette® application met the statutory criteria for a three-year exclusivity award. Novartis hereby incorporates by reference the Yingling Letter into these comments.⁷

In the summer of 1996, FDA also approved Rx-to-OTC switches for two transdermal patch nicotine substitution products – Nicotrol® and Nicoderm® CQ. FDA awarded both products three years of exclusive marketing under the Waxman-Hatch Act.⁸ In March 1997,

³ The product was marketed as a prescription product under a joint venture between HMR and SmithKline. HMR apparently transferred the ownership of the underlying NDAs to SmithKline sometime prior to the February 1996 Rx-to-OTC switch approval as the FDA’s reference, Approved Drug Products with Therapeutic Equivalence Determinations, 20th Edition (2000) (hereafter: “The Orange Book”), names SmithKline as the holder of the NDA under which the OTC switch was approved.

⁴ Public Law 98-417; 98 Stat. 1585 (1984).

⁵ The Nicorette OTC switch approvals were actually for supplements to the NDA’s covering the 2 mg. (N18612) and 4 mg. gums (N20066).

⁶ To the best of our knowledge, FDA’s position on three-year exclusivity for Rx-to-OTC switches has not changed since FDA issued the Yingling Letter in October 1996. While we will discuss in greater detail in these comments why the Greenberg Petition should be denied, a straightforward review of the Yingling Letter makes clear that the Greenberg Petition does not raise any novel issue of fact or law that would preclude a grant of exclusivity to Habitrol, assuming that as Habitrol®’s sponsor, NCH, can satisfy the statutory language governing exclusivity. NCH has done so. See Part II of these Comments.

⁷ See Docket No. 95P-0366.

⁸ The sole explanation in prior editions of the Orange Book as to why FDA granted exclusivity to the Nicotrol® and Nicoderm® CQ Rx-to-OTC switch NDAs (20165 and 20536) was that they constituted “new products” (indicated in

although FDA had already approved both the Nicotrol® and Nicoderm® CQ switch applications and also had already awarded both products exclusivity,⁹ the Greenberg Petition was filed. That petition asked FDA to deny exclusivity to all nicotine substitution products that sought a switch from Rx to OTC use. The Greenberg Petition has been pending since that time.

NCH submits these comments in support of FDA's consistent application of the grant of market exclusivity to those Rx-to-OTC switch products that, like Habitrol®, have fulfilled the statutory requirements for an exclusivity award.

Since the Greenberg Petition was filed, on December 23, 1998, the agency approved the Rx-to-OTC switch application of another nicotine substitution product, Elan's NTS™ (nicotine transdermal system).¹⁰ According to the Orange Book, the Elan Rx-to-OTC Switch either has not been awarded exclusivity or a decision has not yet been made as to its entitlement.^{11 12}

(Footnote cont'd from previous page.)

the Orange Book by a "NP" designation). Presumptively, that exclusivity, because it was three years in length, had to have been based on one or more of the following statutory exclusivity clauses: 21 U.S.C. §§ 355(c)(3)(D)(iii), 355(c)(3)(D)(iv), 355(j)(4)(D)(iii), or 355(j)(4)(D)(iv), which all contain identical qualifying language requiring, in summary, that, to get exclusivity, the application must have contained new essential clinical investigations conducted or sponsored by the applicant. As these products did not involve any change other than that of switching from Rx to OTC availability, the FDA's "new product" categorization must be based solely on the Rx-to-OTC switch being supported by new clinical investigations essential to approval. NCH knows of no reason to treat Habitrol® any differently.

⁹ NCH could not locate evidence of exactly when FDA made the decisions awarding exclusivity to OTC Nicotrol® and Nicoderm® CQ. However, those awards were made at least by January 31, 1997, as both awards are listed in the exclusivity addendum to the 17th Edition of the Orange Book, which contained information current through that date. Now that those awards have expired, and in view of the fact that the Agency has not yet replied to the Greenberg Petition, the petition arguably is moot as to Nicotrol® and Nicoderm® CQ.

¹⁰ NDA 19983; supplement approved on December 12, 1998. As a prescription product, Elan's product was sold under the trade name, Prostep®, and was distributed by Wyeth-Ayerst Laboratories. We understand that, as an OTC product, the product will be distributed by Perrigo.

¹¹ See Exhibit B. See also http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexcl.cfm?Appl_No=019983&Product_No=003&table1=OTC

¹² Agency officials have informed us that, as a matter of policy announced in the preamble to a 1989 proposed rule [54 Fed. Reg. 28872, at 28901. July 10, 1989], exclusivity denials are not published in FDA's Orange Book or otherwise communicated to a person seeking exclusivity. Rather, we were told, if a person wants to learn that its exclusivity has been denied, the person must (a) review the Orange Book and, (b) upon noting that its own NDA approval (to which a claim of exclusivity relates) has been published in the Orange Book, must then (c) review the appendix to the Orange Book to see if a positive exclusivity decision has been published at the same time. If the NDA applicant, upon seeing its approval, does not find a corresponding entry elsewhere in the Orange Book awarding it exclusivity, the applicant can then infer that its exclusivity has been denied. Such an "unnoticed" denial fundamentally corrupts the due process clause of the U.S. Constitution, the Administrative Procedures Act, and the Federal Food, Drug, and Cosmetic Act.

On November 12, 1999, FDA approved supplemental NDA 20-076/S011 for NCH covering the OTC marketing of Habitrol®. Earlier this summer, NCH learned verbally from agency officials that NCH's request for exclusivity for OTC Habitrol® had been denied. NCH has requested FDA to reconsider that decision. In conjunction with this request and because the Greenberg Petition is still pending and to ensure a full and complete record with respect to all related issues, NCH is submitting these comments.

II. THE LEGAL STANDARD FOR THREE-YEAR EXCLUSIVITY AND ITS APPLICATION TO A HABITROL® RX-TO-OTC SWITCH NDA APPROVAL

Before addressing specific issues raised in the Greenberg Petition, we will first review the state of the law relative to three-year exclusivity and discuss why, upon the approval on November 12, 1999, by FDA, for an Rx-to-OTC switch¹³ of Habitrol®, three-year exclusivity should have been granted.

A. The Statutory Language

In order to qualify for three-year exclusivity, the Rx-to-OTC switch applications of Nicorette®, Nicotrol® and Nicoderm® CQ each had to separately satisfy the Waxman-Hatch Act's provisions on exclusivity which, in pertinent part, award exclusivity to a new drug application (or a supplement thereto) approved under § 505(b) of the Act that contains:

... reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant.

21 U.S.C. § 355(c)(3)(iii) and (iv).

The statute provides no further discussion of what Congress meant by the precise language of the three-year exclusivity provision, particularly the key terms "new," "clinical investigations," "essential to the approval of the application" and "conducted or sponsored by the applicant." Recognizing that this and other parts of the statutory language of the Waxman-Hatch Act would require further development through rule-making, Congress directed FDA to promulgate regulations to implement the 1984 law. FDA implemented the exclusivity parts of the statute in October 1994.¹⁴ Rather than discuss FDA's regulations in their abstract, these

¹³ As will be discussed in greater detail later in these comments, because NCH has proven that its OTC Habitrol® is effective for an eight-week course of treatment as opposed to the ten weeks approved for Habitrol® as a prescription product, this NDA supplement, in the agency's view, technically may not be an Rx-to-OTC "switch" at all. For convenience's sake, NCH nonetheless will refer to this supplement as involving an Rx-to-OTC switch.

¹⁴ 59 F.R. 50337 (October 3, 1994); 21 C.F.R. § 314.108.

comments will establish that, when applied to the Habitrol® Rx-to-OTC switch application, FDA should grant exclusivity to that switch. Thus, FDA also must deny the Greenberg Petition.

B. Because NCH Sponsored The New Clinical Investigation Essential to the Approval of a Switch from Rx-to-OTC Labeling, Habitrol® Is Entitled to Three Years of Exclusivity

The Greenberg Petition concedes, at page 18, that:

...[E]xclusivity for Habitrol® should rest solely on whether Ciba Self Medication [now NCH], the sponsor of the OTC switch NDA (#20-076-S011) for Habitrol®, performed its own essential and new clinical investigations.

We agree. Indeed, this statutory requirement was applied by FDA to the Rx-to-OTC switch applications of Nicorette®, Nicotrol®, and Nicoderm® CQ. Thus, because NCH has performed the statutorily required new essential clinical investigation to support the Habitrol® switch (in this case, study CCP 94-002), it should have been awarded three years of exclusivity.

1. The 1994 Guidance Requires New Clinical Investigations to Justify Many Different Aspects of OTC Nicotine Substitution Products, Including Proving the Comparable Efficacy of the OTC Product to the Original Prescription Formulation

On March 1, 1994, the agency issued a draft guidance entitled "Requirements for Approving OTC Nicotine Substitution Products."¹⁵ In that guidance, FDA stated:

...[T]he basic presumption which needs to be established by substantial evidence derived from adequate and well controlled studies is that adequate directions can be written for safe and effective use of the product by consumers.

Id. at 1.

The guidance continued by saying that those adequate directions for OTC use needed to accomplish, *inter alia*, a showing that the OTC nicotine substitution product¹⁶ could "***achieve comparable efficacy to 'average' treatment with prescription products.***" Id. (Emphasis added.)

¹⁵ Issued by the Pilot Drug Evaluation Staff & Office of OTC Drug Evaluation, CDER, FDA.

¹⁶ The guidance applies to all nicotine substitution products proposed for switching from Rx to OTC status, regardless of dosage form. For convenience's sake, NCH hereafter will refer to transdermal nicotine substitution products as "nicotine patch(es)."

The guidance document also articulated other factors a sponsor would have to show to secure approval of an Rx-to-OTC switch of nicotine patches. These included demonstrating that (1) consumers could self-select themselves for treatment; (2) consumers could identify and deal with emergent treatment signs and symptoms; and (3) the product was resistant to misuse, abuse or chronic use for other indications that might pose a risk to the public. The agency made clear that, to satisfy the guidance, would require more than one type of study:

Previous experience has shown that no single trial can effectively meet such varied requirements and therefore they will be best met by selecting appropriate patient populations for their differing objectives.

Id. at 1.

Thus, FDA set a fairly high “bar” for an Rx-to-OTC switch of a nicotine substitution product and anticipated that several different types of studies might be required to justify a switch. The question relative to NCH’s entitlement of exclusivity is whether any such study conducted or sponsored by NCH meets the statutory/regulatory requirements of “essential new clinical investigations.” As mentioned, study CCP 94-002 does.

2. NCH Conducted a New Essential Clinical Investigation That Compared the Efficacy of Habitrol® When Used Under OTC Conditions Against Its Use Under Prescription Dispensing and, Thus, Is Entitled to Exclusivity

a. The Rx-to-OTC Comparable Efficacy Study Is A *Clinical* Investigation

FDA regulations define “clinical investigation,” at 21 C.F.R. § 314.108(a), as:

[A]ny experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects.

Put simply, if, in the course of an experiment, human subjects use the drug, that experiment meets the definition of a clinical study. Thus, it is clear that OTC usage studies are clinical investigations for purposes of Waxman-Hatch Act three-year exclusivity.¹⁷

¹⁷ See Yingling Letter, at 4-5. See also, CDER Manual of Policy and Procedure (MAPP) #6532.1, at page 2, which describes an “OTC drug actual use study” as “a controlled experiment in which a prescription drug or an unapproved new drug is used by subjects under OTC-like conditions.” Because the drug is actually used by subjects, an OTC drug actual use study clearly meets the regulatory definition of a clinical investigation established in 21 C.F.R. § 314.108(a).

In this case, NCH performed an OTC usage study to meet FDA's 1994 guidance requirement that it compare efficacy under OTC conditions to that achieved via prescription dispensing. This Habitrol® OTC usage study is a "clinical investigation" for purposes of the Waxman-Hatch Act. Indeed, in the Yingling Letter, in rejecting an assertion that OTC usage studies were comparable bioavailability studies, FDA recognized explicitly that OTC actual use studies are clinical investigations for Waxman-Hatch purposes:

Although clinical investigations were conducted by the sponsor to show, among other things, that Nicorette's efficacy when used by a consumer without the intervention of a physician is comparable to its efficacy under average prescription use, it was clearly not the purpose of these investigations to show comparable bioavailability. Rather, the purpose was to show that differences in patient populations and the way the product is used OTC (i.e., without the intervention of a physician) would not affect Nicorette's efficacy relative to prescription use.

Yingling Letter, at 5. Similarly, the Habitrol® efficacy study, which investigated the actual use of Habitrol® in an OTC setting, is a clinical investigation.

b. The Rx-to-OTC Comparable Efficacy Study Is A *New* Investigation

For Waxman-Hatch exclusivity purposes, FDA defines "new" relative to clinical investigations in a non-temporal manner. A new study is not one done recently in time. Rather, under 21 C.F.R. § 314.108(a), an investigation is new if it is:

... An investigation in humans the results of which have not been relied upon by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.

In lay terms, if FDA has not used a study before to support an approval, it is new.¹⁸ NCH's clinical investigation – CCP 94-002 – satisfies the "new" requirement.

¹⁸ The first instance in which the agency articulated this view was in finding that a study done in 1969 was "new" for purposes of granting exclusivity to a supplemental NDA approved in 1986 for a new indication for Persantine® (dipyridamole). See FDA Docket 87P-0118, August 9, 1988 letter of FDA Associate Commissioner for Regulatory Affairs, John M. Taylor, to the law firm of Bass & Ullman.

- (1) **The efficacy study has never been used to show substantial evidence of effectiveness of any other previously approved drug product.**

Given the fact that Habitrol®, prior to the November 12, 1999 approval of OTC marketing, remained available solely by prescription, it is axiomatic that a study such as CCP 94-002 done by NCH concerning Habitrol® that explored its use OTC could NOT have been used to show substantial evidence of any other approved drug product. In addition, NCH has never submitted CCP 94-002 in support of any other drug product or in any filing prior to this supplement.

Put perhaps more directly, if a person is required – as NCH was here – by FDA to do a study on a prescription formulation to, in turn, support the OTC marketing of the same pharmaceutical formulation, the resulting study of the formulation's OTC use logically could not have been used before for any purpose as its goal is aimed at developing data supporting a new product – an OTC product.¹⁹

- (2) **The efficacy study does not duplicate the results of any investigation relied on previously by the agency to approve any other drug.**

It also is axiomatic that the comparable efficacy studies of Habitrol® in both OTC and prescription use, performed as CCP 94-002, did NOT duplicate the results of any investigation relied on previously by FDA. This conclusion is obvious because no other study exists, other than those in the now-approved Habitrol® Rx-to-OTC switch supplemental new drug application file, that compare Habitrol® as an OTC product versus Habitrol® as a prescription drug. Thus, study CCP 94-002 conducted by NCH is a “new” investigation.

c. The Rx-to-OTC Comparable Efficacy Study Is An *Essential* Investigation

To be “essential to approval” under 21 C.F.R. § 314.108(a), means that, “with regard to an investigation, that there are no other data available that could support approval of the application.” In applying this definition, FDA has consistently taken the approach that, if the application could be fully approved without a particular investigation, then that investigation (that was not needed to secure approval) could not be essential to approval. However, if without the investigation, FDA could NOT approve the application, but could approve it when considering the investigation, the investigation must be essential.

¹⁹ Which is why the agency, in awarding exclusivity to the OTC switches of both Nicotrol® and Nicoderm® had no logical or legal choice but to regards these OTC products as “new” when compared to their otherwise identical prescription forebears.

Applying this standard to the real example of the Rx-to-OTC switch of Nicorette®, the agency made clear in The Yingling Letter that comparable OTC vs. Rx studies were essential to approval:

The agency disagrees with your statement that the studies conducted by the Nicorette sponsor were not essential to the approval of the Nicorette Rx to OTC switch supplements.

Essential to approval means that there are no other data available that could support approval of the application (21 CFR 314.108.) In determining whether a clinical study is essential to the approval of a supplement, there are two relevant considerations. First, the data generated in the clinical study or studies must be necessary to support the safety or efficacy of the proposed change. Second, there must not be published reports of studies other than those conducted by or sponsored by the applicant, or other information available to the Agency, sufficient for FDA to conclude that the proposed change is safe and effective....

The Agency has determined that the data generated in the clinical studies conducted by the Nicorette sponsor were necessary to support the safety of the drug product for OTC use and to demonstrate that the efficacy of the product was within acceptable parameters. Moreover, these data did not duplicate other data in the NDA or publicly available literature.

Yingling Letter at 5 (emphasis in original).

The studies deemed “essential” by FDA in the Nicorette case are the same type of comparable OTC vs. Rx studies conducted by NCH in support of the Habitrol® Rx-to-OTC switch supplement. Moreover, the Habitrol® study was conducted in response to the 1994 Guidance, which established that proof of comparable efficacy of the product when used OTC relative to its effectiveness as a prescription product was required for approval. Thus, it is clear that study CCP 94-002, which NCH submitted to support the approval of supplement S011, and which showed Rx-to-OTC comparability, meets the definition of being “essential” because it is necessary to support a conclusion on the efficacy and safety of Habitrol® as an OTC product. Moreover, CCP 94-002 does not duplication any data previously in either the Habitrol® NDA, the NDAs of any of the other nicotine patch products, or the published literature.

3. The New Essential Clinical Investigation That NCH Conducted Also Supported a Second and Distinct Major Change In the Labeling of Habitrol® – the Duration of the Course of Therapy – and, Thus, Is Entitled to Exclusivity

A separate and distinct basis also exists for FDA to grant exclusivity to NCH relative to this supplemental NDA. Specifically, NCH has proven, in its pivotal study CCP 94-002, that

Habitrol® is effective as an OTC product when used for a duration of eight weeks. In contrast, the approved prescription labeling requires the patient to continue the use of Habitrol® for ten weeks. This change in duration of use alone, when supported by a new essential clinical investigation, warrants a grant of three-year exclusivity by FDA.

There can be little doubt that changing the duration of use of a prescription product when switching to OTC status is a significant change. Indeed, where there is a duration of use change, FDA itself has stated that an "Rx-to-OTC switch" has not even occurred. Rather, the "switched" product there, in the agency's view, constitutes the "initial marketing of an OTC product" because a duration in use difference renders the product distinctly different from its prescription ancestor. FDA's position on this issue is clear from its Manual of Policy and Procedure (MAPP) #6020.5, which governs internal agency procedures for reviewing Rx-to-OTC switches. The MAPP contains the following illustrative definitions that show that changing the duration of use of a prescription product in securing OTC marketing creates a totally new product:

Rx to OTC Switch. This refers only to OTC marketing of a product that was once a prescription product for the same indication, strength, dose, duration of use, dosage form, population, and route of administration.

Initial Marketing of a Drug Product OTC. This category of product could be one of two types: (1) OTC marketing of a product that was never previously marketed as a prescription drug product or (2) OTC marketing of a product in a strength, dose, route of administration, duration of use, population, indication, or dosage form different from ones previously approved for prescription use.

FDA MAPP #6020.5 at p. 2. (Emphasis added.)

Given that no other OTC (or Rx) nicotine patch product is approved for an eight-week duration of use²⁰ and that NCH conducted the pivotal study CCP 94-002 that proved the safety and effectiveness of Habitrol® for that shorter duration of use, NCH has conducted a new, essential, clinical investigation to support a major change in the Habitrol® product that had been

²⁰ For the sake of this discussion and without admitting its validity, we are assuming that FDA would not require an already-approved generic version of an Rx reference listed drug (RLD) such as Habitrol® to conduct a new bioequivalence study to support the switch of it's the Rx generic product to OTC status once its RLD is approved for OTC status. However, as separately discussed in Part II-B-3 of these comments, as NCH has proven that Habitrol is effective as an OTC product via a shortened course of therapy (8 weeks as an OTC vs. 10 weeks as an Rx product), NCH would assert that a new bioequivalence study may be appropriate before FDA may approve an equivalent generic OTC version of Habitrol®. Any greater discussion of that issue will be reserved for a future filing with the agency, if necessary.

marketed as a prescription-only product. NCH, thus, also qualifies for exclusivity under the Waxman-Hatch Act because this supplement contains a new essential clinical investigation that proves Habitrol® can be used under OTC conditions for a shorter duration of use than currently approved for prescription dispensing.²¹

C. In Summary, the Habitrol® Rx-to-OTC Switch Investigation Supports Not One, But Two Major Changes in the Conditions of Use for Habitrol®, Each One of Which Alone Would Warrant Exclusivity

As the Greenberg Petition conceded, exclusivity for Habitrol® should rest “solely on whether [NCH] the sponsor of the OTC switch ... for Habitrol®, performed its own essential and new clinical investigations.” As shown, NCH’s pivotal new clinical investigation, CCP 94-002, is essential to the approval of two major changes in Habitrol®’s conditions for use.

First, CCP 94-002 proved, for the first time, that the effectiveness of OTC Habitrol® compared favorably to that of Habitrol® when used as a prescription product and that its use could be properly administered by a patient without the instruction of a physician. That major accomplishment alone justifies an award of exclusivity.

Second, Habitrol® study CCP 94-002 demonstrated comparable efficacy, under OTC conditions, in a shorter course of treatment than that which was approved for the prescription version of Habitrol®.

The statute dictates, therefore, that upon approval of its supplement to switch Habitrol®, NCH should have been awarded three years of market exclusivity. Such a grant is consistent with the law, fact, and sound public policy.²²

²¹ Given the health concerns associated with nicotine intake from any source, this shorter use period also represents a significant potential health benefit for Habitrol® users seeking to minimize their intake of nicotine, but still participate in a smoking cessation program involving a nicotine replacement.

²² OTC availability of drugs previously available only by prescription serves the public health by reducing the overall cost of medical care (e.g., via cutting doctor bills), possibly by as much as \$20 billion each year. See “Now Available Without a Prescription,” FDA Consumer. November 1996. Thus, having incentives such as market exclusivity available to encourage switches is clearly in the public interest.

III. FDA ABUSED ITS DISCRETION AND ACTED ARBITRARILY AND CAPRICIOUSLY IN DENYING EXCLUSIVITY TO NCH FOR THE OTC MARKETING OF HABITROL AS APPROVED IN NDA 20-076/S011

A. Procedural Background

In supplement S-011, NCH submitted new essential clinical investigations conducted or sponsored by NCH that proved, for the first time:

- (a) that Habitrol® was effective for use as a smoking cessation agent over a course of therapy of just eight (8) weeks [the previous Habitrol® prescription labeling covered a course of therapy that could range from eight weeks to 16 weeks]; and
- (b) that Habitrol® was safe and effective as an OTC product without the intervention of a physician [until the S-011 approval, Habitrol® required a doctor's prescription].

By letter dated November 12, 1999 (copy at Exhibit C), FDA approved S-011 allowing NCH to market the drug for the first time as an OTC product. The approval letter did not address a previous NCH request that it be awarded three years of market exclusivity under the Waxman-Hatch Act.

On November 17, 1999, NCH filed a detailed submission with FDA as to why it was entitled to exclusivity for the S-011 approval (a copy of that submission is attached as Exhibit D to this letter and is hereafter referred to as the "November 17 Letter"). In June of this year, having heard nothing from FDA as to the merits of its claim of exclusivity since filing the November 17 Letter, NCH contacted CDER officials and learned verbally – and for the first time – that its request for exclusivity had been denied, apparently several months previously.²³

However, because no written communication had been issued to NCH replying to its November 17 Letter,²⁴ NCH was unable to understand or meaningfully react to the merits of the agency's exclusivity denial until, well after the decision was made, NCH was provided copies of what we understand is the entire administrative record relating to the agency's erroneous decision to deny exclusivity to NCH. The three documents provided NCH are attached as Exhibits E, F and G, respectively, to this letter. They are:

- An eight-page Exclusivity Summary (on Form OGD-011347) completed by the Division of Over-the-Counter Drug Products (within the Office of Drug

²³ We can not state with precision when the agency's decision to deny exclusivity was made because the only document that reflects a final determination lacks a date as to when it was executed (see Exhibit G).

²⁴ See Note 12 for a description of FDA's procedure for notifying persons requesting exclusivity of the agency's decisions on such requests.

Evaluation V) and signed on February 18, 2000, by Dr. Charles Ganley (Exhibit E);

- A one-page February 22, 2000 memorandum from Dr. Ganley to Mary Ann Holovac, HFD-93, discussing Question #2 of the Exclusivity Summary, together with copies of labeling for Habitrol and a similar product subject to a full NDA, Nicoderm® CQ (Exhibit F²⁵); and
- A one-page undated Exclusivity Determination Checklist signed by Gary Buehler, as Director, Office of Generic Drugs (Exhibit G).

The administrative record we will discuss below is fundamentally flawed for many reasons. One of the most glaring is that, nowhere in that record, do any indicia exist that suggest that FDA reviewed and addressed any of the points offered by NCH in its November 17, 1999 letter to the NDA file supplementing its prior requests for exclusivity.

B. FDA's Failure To Grant Exclusivity To NCH Violates The Plain Meaning Of The Waxman-Hatch Act

In the November 17 Letter, NCH provided a statutory point-by-point analysis of why, under the Waxman-Hatch Act, it was entitled to a three-year exclusivity grant for the approval of S-011. That discussion is essentially replicated above as Part I of these comments. And, while that discussion, on its own, proves that NCH should have gotten exclusivity for the approval of Supplement S011 to NDA #20-076, NCH also recognizes that, while the administrative record is defective and scanty, it does contain some statements or conclusions about Habitrol® that require separate review to show that FDA's views are invalid and Habitrol® should have received exclusivity.

1. The Waxman-Hatch Criteria Were Met

Under the plain meaning of the law, NCH has met all the statutory and regulatory requirements for three-year exclusivity – i.e., the supplement contained new, clinical investigations conducted or sponsored by NCH that were essential to approval. Not only has NCH satisfied the statutory criteria, but it did so while proving not one, but two major new conditions of use for Habitrol® – (a) the switch from Rx to OTC condition of use and (b) the change in dosing regimen to just an 8-week course of therapy.

²⁵ The copies of the labeling attached to the February 22 Ganley memorandum and included in this letter are the best available of the copies provided to us by agency officials.

a. The Rx-to-OTC Switch Alone Warranted Exclusivity

The detailed review of the statutory criteria for exclusivity provided by NCH in the November 17 Letter – and included in Part II of these Comments – makes clear that the agency would not have allowed NCH to change its labeling to provide for the OTC use of Habitrol® had NCH not done a new clinical investigation. NCH did such an investigation and it was essential to the approval of the supplement.

Rather than follow the statute, the agency's decision to ignore the right of NCH to be granted exclusivity on Habitrol® appears to be based on the subjective assessment of the nature of a change covered by a supplement²⁶ that otherwise satisfies the three-year exclusivity provision. In doing so, FDA disregards the fact that an Rx-to-OTC switch alone – even without any other change in labeling – is entitled to three years exclusivity upon satisfying the “*new-clinical investigation-essential to approval-conducted or sponsored by the applicant*” analysis.²⁷ Thus, to the extent that the agency's decision may be based on a rejection of the concept that an Rx-to-OTC switch approval itself is not a significant enough change, it is faulty and without any statutory basis.

The simple fact is that NCH could not have secured FDA approval of this switch without doing clinical investigations.²⁸ And, as FDA itself has concluded – as reflected in the Exclusivity Summary attached as Exhibit E – these investigations were new, clinical, essential to approval and conducted or sponsored by the applicant. The Waxman-Hatch Act does not permit the agency to examine any other factor in deciding whether to award exclusivity.

b. The Change In Dosing Schedule Proven in The Clinical Investigations in S-011 Gives FDA a *Separate And Distinct Basis* to Grant Exclusivity to Habitrol®

²⁶ The same “new-clinical investigation-essential to approval-conducted or sponsored by the applicant” analysis applies to both three-year exclusivity decisions under 21 U.S.C. § 355(c)(3)(D)(iii) and 21 USC § 355(j)(5)(D)(iii) for changes achieved via an NDA and to, as happened here with S-011, exclusivity decisions under 21 USC § 355(c)(3)(D)(iv) and 21 USC § 355(j)(5)(D)(iv) relative to a supplement to an NDA because the statutory language is the same in all those clauses.

²⁷ See Yingling Letter.

²⁸ Indeed, FDA *asked* NCH and the other holders of full NDAs for the various different types of smoking cessation products to perform clinical investigations to switch to OTC status. See, “Requirements for Approving OTC Nicotine Substitution Products,” March 1, 1994, attached to the November 17 Letter and to these Comments, both as Exhibit A. The need for clinical studies was also restated by agency officials Curt Wright and Mary Lambert in a meeting with NCH officials prior to the submission of the studies subject to S-011. During the course of that meeting, NCH was assured by the agency that, by performing clinicals to support the Rx-to-OTC switch, it would qualify for three-year exclusivity.

The November 17 Letter separately set forth why the dosing schedule change proven by the clinical investigations contained in S-011 was a separate and distinct basis for exclusivity. FDA has characterized this change as “not significantly different” (see Exhibit G).

Even if NCH accepted the concept that FDA was authorized under Waxman-Hatch to examine if a change supported by clinical investigations was significant, the agency’s decision to regard the dosing schedule change achieved here as insignificant is arbitrary and capricious as it ignores (if it ever considered) the significant public health advantages of establishing eight (8) weeks as the fixed and non-variable length of treatment for a nicotine cessation product. Among the factors that FDA overlooked is that the change from a length of therapy of up to 16 weeks to just eight weeks via OTC dosing accomplished at least the following obvious public health benefits:

- ◆ reduced the amount of time a consumer is exposed to a substance that the agency has ruled is **addictive**;
- ◆ reduced the amount of time a consumer is exposed to a substance that is a known **carcinogen**;
- ◆ **eliminated the potential variations** in treatment length that existed under the Rx Habitrol® labeling, which improves consumer compliance with labeling instructions and usability; and
- ◆ **made more readily available another therapeutic option**, thus giving consumers more choices on smoking cessation products.

While other advantages to a fixed 8-week regime exist, any of these above should be seen as significant.

NCH is confused how the agency could assert the Habitrol® Rx-to-OTC switch – with or without a dosage change²⁹ – was anything but a significant clinical achievement as the agency’s own statements undermine the position apparently taken in the exclusivity denial. Specifically, in the recently-issued *CDER 1999 Report to the Nation*, on page 12, the agency reviews last year’s accomplishments of its overall OTC Drug Review efforts. Prominently listed there is the new drug approval of the switch of Habitrol® to OTC status (see excerpt attached as Exhibit H).

²⁹ As to the question of whether a dosing change, per se, warrants an exclusivity award, while NCH maintains that the nature of a change is irrelevant to the statutory exclusivity analysis of “new-clinical investigation-essential to approval-conducted or sponsored by the applicant,” NCH is aware of at least one situation where an arguably “insignificant” dosing schedule change garnered the applicant three-year exclusivity. Specifically, NCH understands a supplement to the NDA for OTC Pepcid AC was approved that provided for a change in dosing instructions from “take 1 hour before a meal” to “take 15 minutes to 1 hour before a meal.” This change earned McNeil Laboratories three years of exclusivity. NCH can not fathom any legal, policy, or equitable grounds for FDA to treat its S-011 approval any differently.

FDA's denial of exclusivity to Habitrol® also contradicts how it handled exclusivity for the Rx-to-OTC switches of Nicotrol® and Nicoderm® CQ, two other smoking cessation patch products. Both those applications earned exclusivity for their switches. Thus, from that perspective, the Habitrol® clinical investigations achieved the same Rx-to-OTC labeling change as in the other nicotine cessation patch switches.

2. FDA Is Barred Under Waxman-Hatch From Examining the Nature of a Change in an NDA Supported by Clinical Investigations

While NCH was incredulous to learn that its S-011 did not gain exclusivity for the difficult task of showing Habitrol®'s safety and efficacy as an OTC product, its bewilderment was only compounded when it learned that the change in dosing regimen approved by FDA in S-011 was not "significant" enough to warrant exclusivity (see handwritten note on Exhibit G).

The agency's reliance on the significance of the change in dosing regimen is simply illegal because, in examining the nature of the change, FDA added an extra consideration to the "new-clinical investigation-essential to approval-conducted or sponsored by the applicant" analysis required by the Waxman-Hatch Act. Indeed, Congress addressed the issue of the nature of clinical investigations by specifically excluding – by use of a parenthetical in the statutory language – bioavailability studies from the ambit of a clinical study eligible for exclusivity. Had Congress meant to also exclude clinical studies of Rx-to-OTC switches or clinical studies of "insignificant" dosing regimen changes, it would not have limited the explicit exclusion from "clinical" to just bioavailability studies.

Thus, the statutory language makes clear that if the investigations were "clinical" – as FDA agrees was the case here – then exclusivity is warranted if the other statutory criteria are met even if the clinicals only supported what, in FDA's mind, was a minor change. Indeed, it can be said that Congress answered any question of whether a difference or change was significant when it provided that, to get exclusivity, an applicant had to perform new clinical investigations essential to approval. Put simply, it is solely whether a study is a clinical investigation that Waxman-Hatch examines for exclusivity purposes, not what the study concerned (except for the express carve out for bioavailability studies). Thus, if you had to do clinicals, you have satisfied one key criterion for exclusivity.

FDA is also ignoring the fact that the labeling change from 16 to 8 weeks could only have been accomplished by the filing of new clinical investigations. The agency carefully reviews every label change to a new drug and would not allow a reduction in dosage without proof of effectiveness in the form of clinical data, in this case, new studies. In fact, we are confident that, had NCH decided that it wanted to make the same dosing schedule change covered by S-011 to its prescription Habitrol® labeling, the agency would have insisted that NCH conduct new clinical investigations to support a course of therapy limited to eight weeks.

3. Habitrol® Is Not the Same Drug Product as Nicoderm® CQ; Thus, the Prior OTC Approval of Nicoderm® CQ Is Irrelevant to an Exclusivity Decision for Habitrol®

We anticipate that the argument may be raised that Habitrol® is somehow the same drug product as Nicoderm® CQ or Nicotrol®, both of which were smoking cessation patch products switched to OTC status in 1996 and both of which were awarded exclusivity for those switches. Indeed, the agency's mislaid focus on whether Habitrol® should be considered as the same drug as Nicoderm® CQ is reflected in the February 22 Ganley memorandum attached as Exhibit F. In that memorandum, Ganley raises the issue of whether the slight differences in dosing schedule (presumably between Nicoderm® CQ and Habitrol) are enough to render them the "same."

This question should never have been asked because the agency has long recognized that drug products of different manufacturers are not the same even if in all other respects identical [see, e.g., *U.S. v. Generix Drug Corp.*, 460 U.S. 453 (1983)]. In addition, the inquiry appears to be based on the premise that a prior award of exclusivity to another firm's product has some bearing on the "*new-clinical investigation-essential to approval-conducted or sponsored by the applicant*" analysis that is the sole inquiry relative to exclusivity.

Under FDA's erroneous view, it would assert that where two different drug makers have approval for virtually identical drugs under separate NDAs, if one gets three-year exclusivity for a change, the second can not get exclusivity for the same change even if the second maker had no choice under the law but to conduct new clinical investigations essential to the approval.³⁰

Indeed, under the agency's rationale, once Nicoderm® CQ was approved as an OTC product, NCH should have been able to cease work on its own clinical investigations and rely on the Nicoderm® CQ approval to justify the Rx-to-OTC switch of Habitrol®. However, FDA did not allow NCH to do that. Rather, it required that NCH conduct new clinical investigations and await the review and approval of S-011 before allowing Habitrol® to be marketed OTC.

Moreover, in the case of Nicoderm® CQ, the labeling simply is not the same³¹ as that of Habitrol®. The dosing schedule for Nicoderm® CQ requires a 10-week course of therapy. Habitrol is 20% less at eight days duration. In addition, Step 1 of the Nicoderm® CQ dosing, which has the highest concentration of nicotine (21 mg.), lasts six weeks. With OTC Habitrol®, Step 1 is a mere four weeks. Given these clear differences, NCH fails to understand how the two dosing schedules can be said to be the same.

30

³¹ We presume the agency is using "same" to have its common and usual meaning – i.e., "identical." See Webster's New Collegiate Dictionary, G. & C. Merriman Co., 1981, at page 1014.

Using the Nicoderm® CQ Rx-to-OTC switch as somehow a statutory reason to deny Habitrol® exclusivity also ignores the fact that, unlike with Habitrol®, the Nicoderm® CQ OTC dosing regimen *remained identical* to that of its Rx predecessor. Nonetheless, and on the basis solely of a clinical OTC usage study, the agency awarded exclusivity to Nicoderm® CQ. Thus, based on that example, Habitrol® also warrants exclusivity.

As a matter of fundamental fairness, denying NCH exclusivity under similar, if not more demanding circumstances as presented by the Nicoderm® CQ example, is plainly arbitrary and capricious.

C. FDA'S DECISION IS CONTRARY TO ITS OWN ADMINISTRATIVE RECORD AND, THUS, IS ARBITRARY & CAPRICIOUS.

NCH was surprised when it reviewed the documents provided it as the administrative record relative to the agency's refusal to grant exclusivity to Habitrol® for S-011. Put simply, the documents prove the agency did not follow the plain directions established in its own forms that we must presume were designed to assure that exclusivity decisions were made in strict adherence to the Waxman-Hatch Act statutory and regulatory criteria.

First, let us examine the 8-page Exclusivity Summary attached as Exhibit E. In it, appears the following instruction:

"Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO—please indicate as such)"

[Emphasis added.]

As required by the instructions, this question on the form was initially and correctly answered by a typewritten "X" in the "No" line. This reflects, unquestionably, the view that, because this Habitrol® supplemental NDA involved an Rx-to-OTC switch, checking the "No" line on Question #2 was the only possible option.³²

³² The other key defect associated with any focus on the nature of a product or change to determine exclusivity is that such a concern ignores the Waxman-Hatch Act's clear statutory focus, in the three-year exclusivity provisions, on what an application contains, not what product it covers. In contrast, the five-year exclusivity provision, by its terms, relates to an application with respect to a specific type of drug – i.e., one for which "no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (5). 21 U.S.C. § 355(b)(3)(D)(i). Thus, the five-year exclusivity provision requires an examination of the type of drug covered by the application seeking exclusivity. In contrast, for three-year exclusivity, whether the drug has been previously approved is irrelevant. The sole inquiry is whether the application contained a "*new-clinical*

Some time thereafter, the typed "X" was crossed out and the "Yes" line manually changed. On the copy provided us, then appears an undated³³ handwritten note that we read as saying:

"Per discussion with Don Hare, Nicoderm CQ has received exclusivity. We need to discuss further whether all the of the criteria here have been met. CG"

Directly under that note appears another, shorter, hand written note:

"See attached memo.
2/22/00 CG"

A review of the "attached" memo from Charles Ganley to Mary Ann Holovac (see Exhibit F to this letter) makes clear that the agency then considered a factor beyond those allowed by the Waxman-Hatch Act. Ganley's memo states, *inter alia*:

...I spoke to Don Hare in the Office of Generic Drugs on 2/17/00 about this and he believed that question #2 should be answered "Yes" because Nicoderm CQ was approved for OTC use previously. Both Nicoderm CQ and Habitrol are transdermal delivery systems containing 7, 14, and 21 mg. of nicotine. ***There are slight differences in the directions for use (i.e., dosing schedule).*** It is unclear whether these differences are of a magnitude that they would be construed as being the same or different...

[Emphasis added.]

Thus, Ganley raised, as an issue to be resolved in making the exclusivity decision, the extra-legal consideration of whether the change in dosing schedule was significant.

(Footnote cont'd from previous page.)

investigation-essential to approval-conducted or sponsored by the applicant." NCH's supplement S011 to NDA #20-076 contained such an investigation and, accordingly, is entitled to exclusivity.

³³ When this note was written is not clear. Directly under it, also in hand, but in fainter ink on the copy sent NCH, appears "See attached memo. 2/22/00 CG". Due to the differences in ink of the two notes, we believe they were written at different times.

The answer to Ganley's extra-legal question was provided by Gary Buehler, of FDA's Office of Generic Drugs. In the undated³⁴ one-page Exclusivity Determination Checklist attached as Exhibit G to these comments, Buehler, in conjunction with marking the "NONE" line next to "Exclusivity Recommended," states, without any explanation:

"dosing regimen not significantly different."

Thus, NCH was denied exclusivity, on the basis of five words that involved an inquiry not authorized by the Waxman-Hatch Act.

In addition to considering a factor outside the law, a review of the Exclusivity Determination Checklist indicates that the form itself was not followed. Saliiently, the form bears the following note:

"if any checks appear in the shaded area, it is likely that exclusivity should not be granted. Any exclus. recommendations should be explained below:"

No checks appear in the shaded area of the form provided us.³⁵ Nonetheless, exclusivity was denied.

Accordingly, if one reviews the 8-page Exclusivity Summary as originally completed (i.e., before any interlineations or notes), it is clear that NCH had met each and every statutory requirement for three-year exclusivity and should have been awarded exclusivity. In view of all these deficiencies, the decision to deny exclusivity is patently arbitrary and capricious and should be reversed.

IV. COMMENTS ON THE GREENBERG PETITION

The Greenberg Petition raises an array of points to try to support its view that FDA should deny exclusivity to the applications that supported Rx-to-OTC switches of Nicotrol® and

³⁴ The Exclusivity Checklist Determination form attached as Exhibit G is not dated. Similarly, the interlineations on the Exclusivity Summary are neither dated nor initialed by whomever made the change. Had notations of this sort been discovered during an agency inspection of a regulated manufacturer or clinical investigator, the FDA inspector likely would have listed those practices as violations of Good Manufacturing Practice.

³⁵ The block of the form asking whether the clinical investigations were "New Studies" (in the form, this is actually stated in the converse because the form, instead of asking if the studies are "new," instead asks whether the studies have been relied on by the agency previously) does not appear to be checked at all on the copy we received. However, based on the 8-page Exclusivity Summary that is part of the record, the clear answer should have been "NO", which would have been outside the shaded area – meaning the studies had not been used previously by the agency and thus were "new," reinforcing NCH's entitlement to exclusivity.

Nicoderm® CQ, and NCH's switch of Habitrol®. In our view, these points, whether taken individually or collectively, fail to establish that "switched" nicotine replacement products are not entitled to exclusivity. These comments, thus, will rebut the Greenberg Petition from both a general perspective and, where appropriate, by specific critiques of particular arguments asserted in the Greenberg Petition that are unsupported by law, fact, or both.

A. General Observations

The Greenberg Petition's global defects stem from at least two faulty premises. First, because the petition seeks to bar exclusivity for any already-approved Rx nicotine patch product that might switch to OTC availability, the petition attempts to treat all nicotine patch products as if they were a homogeneous "class" of products to which general principles of safety and effectiveness can be applied. In doing so, the Greenberg Petition applies sweeping conclusions to products of diverse companies without regard to the fact that, whether viewed from a pharmacological, physical, or legal perspective, all are distinctly different products.³⁶

The Greenberg Petition thus ignores not only logic, but established legal precedent that a drug product is not just determined by its active ingredient, but also with respect to all other aspects of the product and its formulation including, but not limited to, route of administration, dosage form, delivery system, labeling, duration of use, as well as the identity and location of the person making the product.³⁷

³⁶ A "class" view of OTC products, where general safety and efficacy conclusions are sought relative to all similarly-situated products, may be appropriate for products such as those that went through FDA's OTC Drug Review, but has no sound legal or public policy foundation in dealing with products originally marketed as prescription products when they are proposed for switching to OTC availability through the NDA process. See also, Pfizer v. FDA, 753 F. Supp. 171 (D.Md. 1990), which approvingly quoted USV Pharmaceutical Corp. v. Weinberger, 412 U.S. 655, 664 (1973), in discussing the definition of "drug product" –

It is true that an NDA covers a particular product or product that it names and that [21 U.S.C. § 355] when applied to an NDA is personal to the manufacturer who files it. Section [355], in other words, addresses itself to drugs as individual products.

Pfizer, at 178.

³⁷ Generix, supra. FDA has reiterated this principle in the context of "180-day" or "ANDA" exclusivity under the Waxman-Hatch Act [21 U.S.C. § 355(j)(4)(D)(iv)]. On December 4, 1998, in a letter from FDA CDER Director, Janet Woodcock, the agency rejected a Torpharm petition that had argued that Novopharm was not entitled to ANDA exclusivity on a 75mg. ranitidine product because a different strength of ranitidine had already enjoyed 180-day exclusivity. Torpharm had petitioned that, because the statute used the term "drug" in the ANDA exclusivity clause, once there was a first commercial marketing of any ranitidine product – even if under a different strength – no subsequent ranitidine approval could qualify for ANDA exclusivity. In denying Torpharm's petition, FDA made clear that:

...FDA does not define drug product to mean active ingredient. Rather, it "means a finished dosage form, for example, tablet, capsule, or solution that

(Footnote cont'd on next page)

Second, by failing to regard the already-approved products as each being a distinctive product, the Greenberg Petition never examined – on a case-by-case basis – whether an award of three-year exclusivity might be valid in any one individual product’s circumstances. However, FDA, upon approving both Nicotrol® and Nicoderm® CQ, concluded that each of those products was entitled to three-year exclusivity. While the grounds of FDA’s decision in awarding these products exclusivity are not published in the Orange Book, the only logical conclusion is that FDA must have recognized that, on each product’s individual merits, each product separately met the criteria for exclusivity under the Waxman-Hatch Act. At minimum, we do know that the agency regarded these OTC products – which were identical in all others respects to their Rx predecessors – as “new products.”³⁸

And, as the Yingling Letter makes clear, many unique aspects, all consistent with the legal requirements for exclusivity, existed in the Nicorette® Rx-to-OTC switch application that provided grounds for FDA to grant exclusivity to Nicorette®’s switch. FDA should continue that same case-by-case analysis relative to the Rx-to-OTC switch of Habitrol®.

B. Specific Comments

In addition to its fundamental global flaws, the Greenberg Petition also contains a number of specific assertions that do not pass reasoned scrutiny.

1. The Safety Of OTC Nicotine Patches in General or Habitrol® Specifically Has Not Yet Been Shown on Such a General Basis as to Preclude the Needs for Clinical Investigations For Nicotine Patch Rx-to-OTC Switches

The Greenberg Petition contains a lengthy argument that sponsors of prescription nicotine patch products no longer need prove, in conjunction with their Rx-to-OTC switch applications, that the OTC use of their products is safe. The petition contends that the necessity to affirmatively perform any safety studies has been obviated since Nicorette® was approved for OTC sale in February 1996 because so much information now exists in the published literature on nicotine and its safe use, particularly relative to smoking as a source of nicotine. In other

(Footnote cont'd from previous page.)

contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.” [quoting 21 CFR 314.3(b)]. Woodcock letter, at pages 2-3.

The agency’s view was upheld last year by the federal courts. *Apotex, Inc. v. Shalala*, 53 F.Supp.2d 454 (D.D.C. 1999), aff’d, 1999 WL 956686 (D.C. Cir. Oct. 8, 1999). We do not see how FDA can resolve its expressed view of “drug” in the *Apotex* case with how it is attempting to treat “drug” with respect to Habitrol®.

³⁸ See Note 8, *infra*.

words, the Greenberg Petition asserts that proof of safety via clinical investigations would be duplicative and unnecessary for any nicotine substitution product.³⁹ The petition's reasoning is flawed both generally and particularly.

- a. Contrary To What The Greenberg Petition Suggests, Proof Of Safety Of One OTC Nicotine Substitution Product Does Not Automatically Extend To Other Nicotine Substitution Products.

Each of the nicotine patch products is a unique product, all listed separately in FDA's Orange Book, even when they all were available solely by prescription. Thus, while the data in one company's OTC switch NDA on safety may be helpful for FDA to reach a general view that nicotine patch products are safe when used OTC, the other company's data do not address the specific question of whether the individual product proposed for switching may be safely used under OTC conditions.⁴⁰ That question can only be explored – as was done with Habitrol® as required by the 1994 Guidance – by comparing the OTC version of a product against the same product's use under prescription conditions. For, as is evident by the agency's classification of the exclusivity decisions relative to Nicoderm® CQ and Nicotrol®, the OTC version of a product is a “new product” warranting exclusivity even if the product in all other respects is the same as when marketed under the prescription legend.⁴¹

- b. The Greenberg Petition Fails to “Prove” The Safety Of Nicotine Substitution Products.

The Greenberg Petition's safety discussion deals extensively with nicotine withdrawal and a smoker's ability to deal with nicotine toxicity. Because smokers allegedly can deal with those challenges, the Greenberg Petition concludes that the safety of nicotine patches has been

³⁹ See Greenberg Petition, pages 7 to 11.

⁴⁰ NCH submits that the Waxman-Hatch Act requires that the agency, in making a determination of exclusivity, must review each manufacturer's product's entitlement to exclusivity separately. Indeed, the agency's handling of exclusivity decisions on these very products when they first were approved as prescription drugs in 1991 is consistent with that view. At that time, in approving both the prescription Nicoderm® CQ (then called simply “Nicoderm”) and the prescription Habitrol® products, FDA awarded each NDA, upon approval, three years of market exclusivity. If FDA were to accept the ill-founded “logic” of the Greenberg Petition that these products are somehow the same for purposes of exclusivity, it arguably would have had to have denied exclusivity – which it did not – to prescription Habitrol® simply because Habitrol® received its approval about three weeks after the Nicoderm® prescription approval in 1991.

⁴¹ But, as discussed in more detail in Part II-B-3 of these Comments (infra, at pages 10-11), the Habitrol® Rx and OTC products do differ in one key material respect – the duration of use. Thus, assuming, *arguendo*, that the Rx vs. OTC status of the two Habitrol® products was not enough to support a claim of exclusivity, another change was endorsed here by FDA that clearly renders OTC Habitrol® a fully distinct and new product from that of prescription Habitrol®.

proven to the point where additional clinical investigations are not needed to show how nicotine patch users can manage adverse events.⁴²

However, all the data cited to support this proposition is based on management by current smokers of nicotine intake. It is not based on how nicotine patch users themselves can manage adverse events. Relying purely on data as to how smokers manage adverse events when considering the safety of smoking cessation products compares two distinctly different sample populations. For there is a plain and fundamental difference between smokers and patch users; namely, the patch user is NOT to be smoking if he/she is following the product's directions for use. Thus, any data generated relating to how smokers manage adverse events does not correlate to how patch users manage adverse effects, as they are patently different subject populations.

The Greenberg Petition's analysis also ignores many of the other objectives that the 1994 guidance required be proven in connection with an Rx-to-OTC switch, such as whether the OTC directions for use would be adequate to permit the patient to self-select for treatment or identify and deal with treatment emergent signs and symptoms. In this respect, it is important to note that the potential "signs and symptoms" associated with nicotine patch use include considerations other than just managing nicotine intake. Indeed, the prescription labeling for Habitrol® included at least seven bolded headings under "Precautions" ranging from "**Allergic Reactions**" to "**Peptic Ulcer Disease.**" Thus, even if the Greenberg Petition arguably had proven that quitters can manage nicotine toxicity, that would address only one small aspect of whether Habitrol® can be used both safely and effectively as an OTC drug.

We do not suggest that studies done on other nicotine patches do not provide helpful collateral information for FDA as to the general safety of the class of products known as nicotine patches. But, to justify a switch of Habitrol® to OTC status, FDA required that NCH show that the frequency of adverse events linked to Habitrol® itself did not increase to any significant degree under OTC conditions when the intervention of a physician is removed. Showing the safety of OTC vs. Rx use of Habitrol®, *a fortiori*, could only have been done in a clinical investigation to be found in the Habitrol® switch NDA because, before being studied under OTC conditions by NCH, an OTC version of Habitrol® simply did not exist. Indeed, the only OTC "version" that was "available" for study before FDA approved the Rx-to-OTC switch of Habitrol® was that product studied under an IND (protocol CCP 94-002) by NCH that eventually was essential to the approval of the Rx-to-OTC switch of Habitrol®. And, contrary to the Greenberg Petition, the safety of OTC Habitrol® could not be proven solely by the data cited in the Greenberg Petition. Rather, FDA insisted that NCH prove that OTC Habitrol® could be used safely compared to the Rx Habitrol®. NCH did so by means of clinical investigations.

Another major safety point raised in the Greenberg Petition is that the safety of OTC use of nicotine patches is proven by five years of use as a prescription product because, in "reality,"

⁴² The Greenberg Petition, at pages 8-9.

there was no involvement of a physician historically in the use of nicotine patches.⁴³ This argument is unfounded on several points. First, that statement in the Greenberg Petition is nothing greater than a bald assertion of the author. The Petitioner offers no citation to any authority to back its claim that there was no physician intervention while Habitrol® – or any other nicotine product – was being dispensed as a prescription product.

Thus, Petitioner's argument that FDA should be able to extrapolate prescription use of nicotine patches to reach a decision on granting OTC uses rests, in a major respect, on Petitioner's unproven assertion that there was no doctor intervention while these products were being used Rx. This premise also makes no sense for an Rx-to-OTC switch because it ignores that one of the basic issues that any Rx nicotine patch NDA holder had to prove to switch to OTC status was to assess whether the lay person can safely diagnose and use that product on an OTC basis.⁴⁴ Clearly, the prescription approval of Habitrol® was not so based, but depended on physician intervention.

In addition, to say that there was no doctor intervention in prescription drug use ignores a fundamental aspect of prescription drug use – that no patient can legally gain access to a prescription drug without first securing a doctor's prescription. As the use of a prescription product thus always legally depends on the intervention of a doctor, extrapolation of allegedly safe Rx use to prove safe diagnosis and use of an OTC product in the absence of a doctor's intervention defies logic.

⁴³ Id., at 10. Petitioner makes this argument to help justify its conclusion that proof of OTC safety has already been proven without the need for any additional studies by NCH.

⁴⁴ 1994 Guidance, at 1-2.

2. The Effectiveness of Nicotine Patches in General or Habitrol® Specifically for OTC Use Has Not Yet Been Proven So as to Preclude the Need for Clinical Investigations For Nicotine Patch Rx-to-OTC Switches

Curiously, the Greenberg Petition devotes little attention to showing that there is no need for clinical investigations into the *effectiveness* of nicotine patch Rx-to-OTC switches in general or Habitrol® specifically. The reason for this scanty treatment of a key issue in the question of whether a Habitrol® Rx-to-OTC switch should get three-year exclusivity is simple: no publicly available data exist, outside the approved Habitrol® Rx-to-OTC switch supplemental NDA, to prove, with substantial evidence,⁴⁵ the effectiveness of the switch of Habitrol® (or any other nicotine patch product) from Rx to OTC availability.

Indeed, the Greenberg Petition offers no evidence of any available clinical investigations that compared the effectiveness of any nicotine patch used under prescription conditions against that same product's effectiveness when used OTC. Rather, as sole support for its assertion that the efficacy of OTC nicotine patches has been proven, the Greenberg Petition offers a meta-analysis⁴⁶ that found prescription nicotine patches were effective over placebo. While that information may be helpful to FDA in assessing the general effectiveness of nicotine patches, it is irrelevant to the specific effectiveness question that the 1994 guidance asked, and NCH has answered, relative to the Rx-to-OTC switch of Habitrol®.

The Greenberg Petition's discussion of the Fiore meta-analysis is also misleading, as the petition contends that the meta-analysis "found that nicotine patches were effective over placebo without regard to professional supervision."⁴⁷ We could find no statement in the Fiore study report that substantiates this assertion in the Greenberg Petition. In fact, a review of that study report makes clear that it did not opine, in any way, on the effectiveness of nicotine patches in the absence of professional supervision.

First, one of the criteria for inclusion in the meta-analysis was that the study involved some level of counseling. Second, there are numerous statements in the published Fiore report that make clear that no conclusions were reached as to the effectiveness of nicotine patches in the total absence of professional supervision (e.g., in an OTC setting). Rather, the Fiore report

⁴⁵ As stated by FDA in the Yingling Letter, while substantial evidence is required for the approval of an NDA, that same level of substantiation is greater than the standard for the award of exclusivity under the Act – which focuses on whether there was a new clinical investigation essential to the approval of the NDA/supplement that was conducted or sponsored by the applicant.

⁴⁶ Fiore, MC, Smith, SS, Jorenby, DE, Baker, TB, "The Effectiveness of the Nicotine Patch for Smoking Cessation: A Meta-Analysis," JAMA, 1994; 271:1940-47. A meta-analysis is, itself, not a clinical investigation, but a composite analysis of the results from other studies.

⁴⁷ Greenberg Petition, at 11.

carefully pointed out that intensity of counseling did not appear to have any impact on the effectiveness of patch use vs. placebo:

It is clear from the results of this meta-analysis that the efficacy of the nicotine patch, relative to the placebo patch, was essentially unrelated to adjuvant intensity.⁴⁸ [Emphasis added.]

At best, therefore, the Fiore meta-analysis supports the use of nicotine patches with minimal counseling. It clearly left open the question of how effective nicotine patches would be without any counseling – such as in OTC use:

Although intensive adjuvant counseling appears to improve overall rates of smoking cessation, such counseling [i.e., intensive] is not critical to ensuring acceptable levels of efficacy. This suggests that a stepped-care approach may be appropriate for smoking similar to that used for hyperlipidemia and hypertension. In such an approach, the patch might be accompanied by little or no counseling in its initial use and with increasing amounts of counseling in re-treatments.⁴⁹ [Emphasis added.]

As to Habitrol®, NCH has answered the question raised by Fiore positively by doing a new essential clinical investigation showing that a nicotine patch product used OTC has comparable efficacy to the same patch used under prescription conditions. Thus, NCH has earned exclusivity under the Waxman-Hatch Act.⁵⁰

⁴⁸ Fiore, at 1945.

⁴⁹ Id., at 1947.

⁵⁰ The Greenberg Petition also contains a lengthy analysis of why the effectiveness studies done by the sponsors of the Rx-to-OTC switches for Nicotrol® and Nicoderm® CQ allegedly were defective. We will not address those analyses in detail because, if the Greenberg Petition is correct in its analyses, and those studies were defective, FDA arguably should not have approved those Rx-to-OTC switches. Thus, some of the new studies that the Greenberg Petition contends already proved the effective use of OTC nicotine patches should be stricken (due to their defects) from any analysis of exclusivity for Habitrol®. If we were to accept the Greenberg Petition's analysis of these Nicotrol® and Nicoderm® CQ studies and "throw out" those studies (and, presumably, Greenberg would also rescind the approved Nicotrol® and Nicoderm® CQ Rx-to-OTC switch NDA approvals as well), then there can be absolutely no question that the studies NCH has done to prove that Habitrol® is effective when used OTC are essential because no other studies, other than those done by NCH to support the Habitrol® Rx-to-OTC switch, would exist for the Agency to even review relative to its exclusivity decision. If Greenberg is wrong in its assertion that these studies were defective, the "success" of the Nicotrol® and Nicoderm® CQ effectiveness studies still should have no bearing on Habitrol®'s OTC effectiveness due to the fact that these products are, both factually and legally, distinctly different drug products from Habitrol®. Indeed, at a bare minimum, absent a showing of bioequivalence between Habitrol and these other products, no such comparison is even remotely scientifically valid, let alone satisfactory on a legal basis.

In addition to addressing the Fiore question of adjuvant intensity, the Habitrol® Rx-to-OTC switch NDA also addressed another issue that the Fiore study identified as having clinical significance:

“Research has not kept pace with the widespread use of the nicotine patch, resulting in many unanswered, but important questions. *For instance, little is known about the optimal duration of patch treatment.* While different studies have used different durations of patch treatment, none has systematically varied treatment duration in the same clinical trial.

[Emphasis added.]

In the case of Habitrol®, the approved labeling for the prescription product allowed for a duration of therapy of up to 16 weeks. In addition, the first step could be as long as eight weeks. These are just the types of variations in duration identified by the Fiore report as presenting important unresolved questions. Clearly, the Habitrol® OTC approval, which reduces the total length of treatment to a fixed 8 weeks and the length of the first step to 4 weeks, has made a significant contribution to resolving the duration question raised by Fiore.

3. FDA’s “Umbrella Policy” on Exclusivity Should Not Be Disturbed

- a. Because NCH is separately entitled to exclusivity, it need not shelter under the umbrella of any other nicotine patch product’s Rx-to-OTC switch exclusivity.

The Greenberg Petition contains a lengthy discussion⁵¹ as to why FDA should disregard the “Umbrella Policy” established in its rule making on exclusivity.⁵² In our view, the Umbrella Policy is not implicated by this situation for several reasons.⁵³ However, to the extent that the agency might treat any of the Greenberg Petition’s points on the Umbrella Policy as meriting attention, NCH offers these general comments on that policy.

First, the policy, by its terms, only can be applied in those rare situations where a change might be desirable to a full NDA where the change itself does not need to be supported by clinical investigations, but still might be important to be implemented promptly and would result

⁵¹ Greenberg Petition, pp. 18-27.

⁵² 54 Fed. Reg. 28871, 28897 (July 10, 1989).

⁵³ For example, the Habitrol® Rx-to-OTC switch application was approved in November 1999, after the exclusivities enjoyed by both Nicotrol® and Nicoderm® CQ had expired.⁵³ Thus, arguably, the applicability of the umbrella policy is moot in this situation as there would be no other exclusivity serving as an umbrella to fall under.

in the creation of a new drug product that would not be the same as the product enjoying exclusivity.

An example given in the rule-making was a dosage form change (e.g., tablet to capsule). If that occurred, the new capsule dosage form would be a separate and distinct product under a separate NDA that would not be protected by any continuing exclusivity that covered the prior tablet version of the product. And, if that exclusivity had not yet expired, there existed the possibility that a generic applicant could file an ANDA using the changed drug as the listed product and the holder of the NDA for the changed drug would have lost the benefit of its hard-earned exclusivity. To prevent that hardship – and presumably to both encourage innovation and not discourage NDA holders from making desirable changes to products – the Umbrella Policy “shelters” the second product under any exclusivity that its sister NDA still enjoyed.

NCH supports the application of the Umbrella Policy in these circumstances. However, in so doing, NCH reiterates that, in this situation, where clinical investigations were required to support the change from Rx to OTC status, NCH qualifies for a separate and distinct exclusivity for the Rx-to-OTC switch that is the subject of this supplement. Thus, there would appear no need to apply “umbrella exclusivity” here because NCH is entitled to primary exclusivity for the very change being effected in this supplement and does not need the “shelter” of any exclusivity that might be enjoyed by any other nicotine patch product.⁵⁴

b. The Umbrella Policy is a Sound Construction of the Waxman-Hatch Act.

The legal basis for applying the umbrella policy to the Habitrol® Rx-to-OTC switch is articulated in detail in FDA’s rule-making documents on exclusivity.⁵⁵ NCH will not repeat those discussions here, especially as the Greenberg Petition does not offer, in our view, any sound legal argument as to why FDA’s construction of the Waxman-Hatch Act – as reflected in the umbrella policy – should be overturned.

The application of the umbrella policy to the Habitrol® Rx-to-OTC switch also would have served sound public policy interests. As shown, Rx-to-OTC switches clearly serve the public interest by reducing health care costs and increasing patient access to safe and effective drug therapies.⁵⁶ As such, switches are encouraged whenever feasible. However, denying

⁵⁴ NCH would assert that, assuming, *arguendo*, if it did need to rely on the exclusivity of another nicotine patch product under the “umbrella policy,” any such exclusivity should be extended, if warranted, under the “pediatric exclusivity” provisions of the FDA Modernization Act of 1997 (Pub. L. No. 105-115, 111 Stat. 2296 (1997), as codified at 21 USC § 355A).

⁵⁵ See note 52, *infra*.

⁵⁶ See note 22, *infra*.

exclusivity to Habitrol® under the Umbrella Policy would have countered that public interest.⁵⁷
58

FDA can avoid these negative impacts on the public's interest in facilitating Rx-to-OTC switches by ensuring that NCH enjoys exclusivity for its Habitrol® Rx-to-OTC switch directly, as NCH plainly has shown it is entitled. Alternatively, to the extent the agency views the Umbrella Policy arguments raised by the Greenberg Petition to not be moot, for the reasons cited above, the agency should not disturb that policy.

⁵⁷ Assuming, *arguendo*, that NCH is not entitled to exclusivity on its own merits for Habitrol®, then the application of the Umbrella Policy here would have served to protect the remaining exclusivity that Nicoderm® CQ then enjoyed because, if NCH had secured approval of its Rx-to-OTC switch supplemental application before the end of the exclusivity period granted to Nicoderm® CQ and NCH had not received any exclusivity, no extant legal or regulatory impediment would have existed to prevent the maker of the approved prescription generic of Habitrol® from itself promptly securing an approval to switch the labeling status of its already-approved prescription nicotine patch product – for which Habitrol® is the listed drug – to OTC status. In that scenario, the generic firm arguably would have been able to enter the OTC nicotine patch market as a generic before the Nicoderm® CQ exclusivity ended. Such a result would negate the exclusivity incentive that Nicoderm® CQ had earned under the Waxman-Hatch Act and illustrates why the Umbrella Policy serves the public interest.

⁵⁸ Second, if NCH does not benefit from any exclusivity – direct or under the Umbrella Policy – that would create a scenario where it might have been in NCH's best interests to delay final approval of this supplemental application until after the exclusivity for both Nicoderm® and Nicotrol® had expired in order to (a) maintain NCH's current unique position as the sole Rx innovator product in the overall nicotine patch market (both prescription and OTC) or (b) to legally ensure that a generic version of Habitrol® did not enter the OTC market any earlier than possible by legally "denying" any generic prescription version of Habitrol® the availability of a listed OTC drug upon which to base a supplemental Rx-to-OTC change. This result, while arguably in NCH's best business interests, would be contrary to the public policy objective of making formerly prescription products available over-the-counter.

V. CONCLUSION

For the reasons stated herein, FDA, upon approving NCH's supplemental application seeking permission to market Habitrol® over-the-counter, should grant NCH three years of exclusivity under the Waxman-Hatch Act. Concurrently, FDA should deny the Greenberg Petition. As of this writing, FDA has not acted on the Greenberg Petition. For the reasons stated herein, NCH submits that FDA should:

1. Formally deny the Greenberg Petition; and
2. Grant three years of exclusivity under the Waxman-Hatch Act to NCH beginning as of the November 12, 1999 approval of NDA #20-076/S011.

If FDA plans to take any action inconsistent with a grant of exclusivity to NCH, we hereby request a meeting with appropriate agency officials prior to the agency taking any final action.

Sincerely,

Novartis Consumer Health



By: David P. Tolman, Associate General Counsel

Exhibits:

- A – March 1994 Draft Guidance
- B. Printout from Orange Book on exclusivity status of Elan's ProStep OTC NDA.
- C – November 12, 1999 Approval Letter (4 pages)
- D – November 17, 1999 Letter (31 pages)
- E – Exclusivity Summary (8 pages)
- F – Feb. 22 Ganley Memorandum + labeling (3 pages)
- G – Undated Exclusivity Checklist Determination (1 page)
- H – Excerpt from CDER 1999 Report (1 page)

A

DRAFT

**Requirements for Approving OTC Nicotine Substitution Products
Pilot Drug Evaluation Staff & Office of OTC Drug Evaluation
Center for Drug Evaluation and Research, FDA**

The Food, Drug and Cosmetic Act¹ assumes a drug for use by humans should be available over the counter (OTC) unless it:

- “(A) is a habit-forming drug to which section 502(d)² applies; or
- (B) because of its toxicity or other potentiality for harmful effect, or method of its use, is not safe for use except under the supervision of a practitioner licensed by law to administer the drug; or
- (C) is limited by an approved application under section 505³ to use under the professional supervision of a practitioner licensed by law to administer the drug.”

All three of the above exceptions are potentially applicable to a consideration of switching nicotine substitution products from prescription to OTC status or qualifying a nicotine substitution product for OTC use without first having it available as a prescription drug.

General guidance on criteria for qualifying a drug for OTC use or switching a prescription drug to OTC status has been offered by the Non prescription Drug Manufacturers Association⁴, Eileen Leonard⁵, Paula Botstein⁶, Carl Peck⁷ and Michael Weintraub⁸.

In the case of nicotine substitution products, the basic presumption which needs to be established by substantial evidence derived from adequate and well controlled studies is that adequate directions can be written for the safe and effective use of the product by consumers. In addition, since nicotine is addictive and in large doses dangerous, as might occur with accidental ingestion by children or pets, any OTC dosage form should not be "abuseable" and should be "safe" to have around small children.

Based on our current understanding of the treatment of individuals who are addicted to nicotine the adequate directions for use need to accomplish the following:

- (1) Permit patient to self-select themselves for treatment appropriately, i.e., selecting self-treatment or consulting a physician, depending on which is indicated by their medical condition(s).
- (2) Achieve comparable efficacy to "average" treatment with prescription products.
- (3) Permit patients to identify and deal with treatment emergent signs and symptoms while using the product, including selecting appropriate self-treatment or consulting a physician depending on which is indicated by their signs and symptoms.
- (4) In addition the product should be resistant to accidental misuse, deliberate abuse, or chronic use for other indications such that it poses an acceptable risk to the public at large.

Previous experience has shown that no single trial can effectively meet such varied requirements and therefore they will be best met by selecting appropriate patient populations for their differing objectives. Smaller trials focusing on groups of patients likely to include a high percentage of

patients who should seek consultation with their physicians would seem best for testing "self-selection" and appropriate "self-treatment" of emergent signs and symptoms (requirements (1) and (3)). Assessing abuseability and safety for children and pets (requirement (4)) would ordinarily require different populations. The detection of adverse events occurring at the 1/1000 incidence level (requirement (3)) and detecting the likelihood of chronic use for other indications (requirement (4)) will require one or more large multicenter trial(s). Such larger trial(s) should also have, as a secondary purpose, confirming the findings from the smaller trials which were focused on the other 3 requirements.

The FDA definition of quit has been 28 consecutive days of self-reported abstinence with biologic verification (usually expired carbon monoxide). An initial 1-3 weeks after quit (grace period) has been accepted in most studies, but the particular 4 week period must be specified in advance. Follow-up to 6 mos (continuous abstinence) is required and follow-up to 12 mos is desirable.

It is our opinion that these studies should be conducted under an IND. The FDA's Pilot Drug Evaluation Staff and Office of OTC Drug Evaluation are prepared to review all protocol designed to meet the above requirements prior to the finalization of the protocols to give an opinion on whether or not the protocols will meet their stated objectives. Even though the IND regulations only require a review of protocols for safety, it is our opinion that agreement on the likelihood that a study will achieve its objectives, before a protocol is finalized, is in an applicant's best interest as well as the public interest.

To expedite review of your proposals, send two copies (one to each OTC and Pilot Drug)
Office of OTC Drug Evaluation, HFD-830
301-594-2226, fax 594-2222
7520 Standish Place
Rockville, MD 20855-
attn: Debra Bowen
Pilot Drug Evaluation Staff, HFD-007
301-443-3741, fax 443-7068
5600 Fishers Lane
Rockville, MD 20857
attn: Sharon Schmidt

-
- ¹ Federal Food, Drug, and Cosmetic Act, as amended, section 503(b)(1).
 - ² Section 502(d) lists the substances which must bear the "Warning - May be habit forming" label. The list does not contain nicotine.
 - ³ Section 505 describes the New Drug Application (NDA) and Abbreviated New Drug Application (ANDA).
 - ⁴ NDMA: Comments to FDA on issues relating to switching prescription drugs to OTC status before the Arthritis Advisory Committee, February 22-23, 1990. [PDES #260]
 - ⁵ Leonard E: Approval of new drug products. Comments before the Dermatologic Drugs Advisory Committee, March 23, 1992. [PDES #261]
 - ⁶ Bostein P: Switching drugs from prescription to OTC through NDAs. Presentation at the Regulatory Affairs Professional Society Meeting, July 17, 1990, 8 pages. [PDES #262]
 - ⁷ Peck CP: Principals of Rx to OTC Switch, Presentation at the Arthritis Advisory Committee, February 22-23, 1990. [PDES #263]
 - ⁸ Weinraub M: FDA's Perspective on Switch Today. Presentation to NDMA Conference on Rx-to-OTC Switch, September 15, 1992. [PDES #]

Corollaries

As the development of OTC smoking cessation aids evolves, we will attempt to collect specific guidances in the list of corollaries which follow.

- a - The first step is to develop (or at least describe in some detail) the complete OTC Intervention Package (PACKAGE). This PACKAGE might include one or more elements of advertising, display, outer carton labeling, individual product wrapper, package insert, video or audio support tapes, printed support materials, referral to support programs, access to telephone support, passive follow-up, price, and barriers to perpetual use.
- b - The ethical sponsor will, after approval, provide the same (or better) support (materials, hot-line, etc.) which comprised the proven PACKAGE.
- c - The price of the PACKAGE and price of any refills is an important parameter. It probably deserves as much consideration in your development plan as the other features of the final PACKAGE. We expect the ethical sponsor to make a good-faith effort to study the PACKAGE at a price which is not substantially different from the post-approval retail price.
- d - Regular use of prescription medications should probably be an exclusion, i.e., be a condition for which the patient should consult their physician. Although a few medications, e.g., theophylline and tricyclic antidepressants, are of particular concern, it may be simpler to specify "regular use of prescription medication".
- e - The US Consumer Product Safety Commission (CPSC), the agency that regulates child-resistant packaging through the Poison Prevention Packaging Act, requests that you inform them of the proposed product, package, and possible hazards. The CPSC is prohibited from releasing trade secret and other confidential business information, 15 U.S.C. 2055(a). Please begin this process as soon as possible as it usually requires a year or more. The CPSC contact is: Susan Barone, 301-504-0477 or 504-0957, fax 301-504-0124.
- f - In assessing the accuracy of self-selection (requirement # 1) for your PACKAGE, consider separately the two types of error, state the target accuracy, and describe how you will iterate your PACKAGE if necessary, i.e., if you do not reach your target. Such assessment can be economically done in settings which would be enriched with high-risk patients, e.g., a cardiology clinic.

		What Patients Actually Did	
		<i>Treat Self</i>	<i>See their MD</i>
What Patients Should Do	<i>Treat Self</i>	CORRECT	Type 1 Error
	<i>See their MD</i>	Type 2 Error	CORRECT

- g - Some high-risk patients (taking prescription medications, pregnant, recent myocardial infarction) will use the medication once it is available OTC (Type 2 Error) and a study design which follows these patients with minimum intervention will provide important safety data.
- h - You may wish to consider retaining some prescription distribution of your product (based on diagnosis or dosage strength) rather than having your product exclusively OTC.

B

Search results from the "OTC" table for query on "019983."

Active Ingredient: NICOTINE
Dosage Form;Route: Film, Extended Release; Transdermal
Proprietary Name PROSTEP
Applicant: ELAN PHARM
Strength: 11MG/24HR
Application Number: 019983
Product Number: 003
Approval Date: Dec 23, 1998
Reference Listed Drug: Yes
RX/OTC/DISCN: OTC
Patent and Exclusivity Info for this product: [Click Here](#)

Active Ingredient: NICOTINE
Dosage Form;Route: Film, Extended Release; Transdermal
Proprietary Name PROSTEP
Applicant: ELAN PHARM
Strength: 22MG/24HR
Application Number: 019983
Product Number: 004
Approval Date: Dec 23, 1998
Reference Listed Drug: Yes
RX/OTC/DISCN: OTC
Patent and Exclusivity Info for this product: [Click Here](#)

Thank you for searching the Electronic Orange Book

[Return to Electronic Orange Book Home Page](#)

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

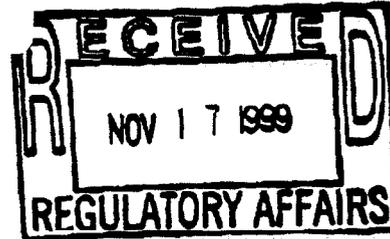
c



Exhibit C

Food and Drug Administration
Rockville MD 20857

NDA 20-076/S-011



NOV 12 1999

Novartis Consumer Health, Inc.
Attention: Mr. Timothy R. Dring
Associate Director, Regulatory Affairs
560 Morris Avenue
Summit, New Jersey 07901-1312

Dear Mr. Dring:

Please refer to your supplemental new drug application dated December 3, 1998, received December 9, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Habitrol (nicotine transdermal system), 21, 14, and 7 mg/day patches.

Please also refer to the Agency approvable letters dated December 31, 1996 and June 2, 1999.

We acknowledge receipt of your submissions dated July 7 and November 5 and 11, 1999. Your submission of July 7, 1999 constituted a complete response to our June 2, 1999 action letter.

This supplemental new drug application provides for the over-the-counter (OTC) marketing of Habitrol (nicotine transdermal system), 21, 14, and 7 mg/day patches to adults (those who are at least 18 years of age) for use as an aid to stop smoking cigarettes. This age restriction is essential to the Agency's finding that this product is safe and effective for OTC use.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted labeling dated November 5, 1999. Accordingly, the supplemental new drug application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the labeling enclosed in the November 5, 1999 submission.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-076/S-011." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submission dated November 11, 1999. These commitments, along with any completion dates agreed upon, are listed below.

You have provided plans for marketing and surveillance designed to ensure that retailers and distributors of your products will only sell them to persons 18 years of age or older, and to include mechanisms, in addition to the proposed labeling, to ensure that the product cannot be sold in any manner or form that would allow a person to obtain the products without first presenting proof of lawful age.

Safety Surveillance:

You have committed to conduct safety surveillance to detect and investigate emergent patterns of misuse and/or abuse of OTC Habitrol, including

- A. monitoring of standard, annual epidemiologic surveys of teenage drug abuse;
- B. monitoring media and wire services;
- C. evaluating all reports to determine if such cases represent a trend suggestive of a larger problem, and making a report of such a problem to FDA along with a proposal for remediation.

Marketing Restrictions and Compliance Surveillance:

You have also committed to marketing the Habitrol Patch in a manner which will ensure compliance with the approved labeling. The plan includes the following elements:

- A. Targeting any advertisement to adult (≥ 18 years) smokers who are motivated to attempt smoking cessation.
- B. Packaging of each patch in child-resistant pouches and of each carton in tamper-evident shrink-wrap, and including a disposal tray in each carton to restrict access to used patches by children or pets.
- C. Restriction of distribution to retail pharmacies, food/grocery stores/supermarkets, mass merchandisers, and club warehouses, the majority of which will be equipped with UPC bar code scanners to assist in compliance with sales restrictions. The products will not be distributed to other channels, including convenience stores or vending machines.
- D. Training of retailers will be provided regarding the marketing restrictions. Measures including random audits will be implemented to monitor retail distribution to detect any instances of product diversion or inappropriate sale. If, through the surveillance program, violations of the conditions of sale are identified the retailer will be retrained to bring the store into compliance, or distribution to the outlet in question will cease.
- E. Encouraging retailers to shelve Habitrol in an appropriate area of the store to deter theft, and to program UPC codes to display a prompt to verify purchaser's age.
- F. Not offering direct-to-consumer "trial size" or "sample" packs.
- G. Making available a free smoking cessation program (toll-free phone number on labeling).

H. Making available a product information program for health care professionals.

As stated in your letter dated November 11, 1999, you agreed to revise the labeling for this drug product at the time of the next printing or within 180 days, whichever comes first, as follows:

1. Delete the statement, "This patch has not been studied in persons under 18 years of age." See D. 12, above and page 7 of the audio tape transcript.
2. In the self-help guide, move the chart on page 21 to page 22 to follow paragraph 2, so that the warnings are not separated.
3. Regarding the self-help guide, page 30, Your Daily Success Calendar, it is still unclear how the smoker (who smokes 10 or less cigarettes per day) can use this calendar. The instructions for the quit day (which day on the calendar), starting dose, and duration of use at that dose should be clearer.
4. Delete the phrases, "NEW NOW WITHOUT A PRESCRIPTION" and "FULL PRESCRIPTION STRENGTH" from all parts of the labeling after the first 6 months of OTC marketing.

Please be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We are waiving the pediatric study requirement for this action on this application.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the labeling directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

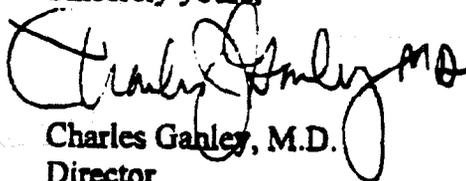
MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

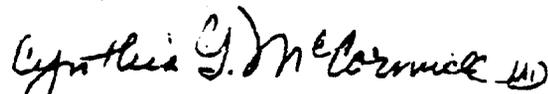
We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

In line with Center for Drug Evaluation and Research policy, oversight of this application is being transferred to the Division of Over-the-Counter Drug Products. If you have any questions, contact Babette Merritt, Project Manager, at (301) 827-2222.

Sincerely yours,



Charles Ganley, M.D.
Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research



Cynthia G. McCormick, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

D



David P. Tolman
Associate General
Counsel

Novartis Consumer
Health, Inc.
560 Morris Avenue
Summit, NJ 07901-1312

Tel 908 598-7661
Fax 908 522 1781

VIA FEDERAL EXPRESS

November 17, 1999

Indira Kumar, Regulatory Project Manager
Food & Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care and Addiction Drug Products
HFD-170
Room 9B-45, Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

Re: **NDA 20-076 Habitrol Approved Supplement 011 – OTC Switch
Supplement/Waxman-Hatch Exclusivity**

Dear Sir or Madame:

Novartis Consumer Health, Inc. ("NCH") submits these comments under NDA 20-076, Supplement 0011, which permits NCH to market its Habitrol® product over-the-counter ("OTC"). These comments are in further support of NCH's prior request that FDA should grant NCH three years of market exclusivity under the Drug Price Competition and Patent Term Restoration Act of 1984 ("the Waxman-Hatch Act")¹ for its OTC Habitrol®.

¹ P.L. 98-417.

November 17, 1999

Page 2

These comments also address the citizen petition filed March 3, 1997, by the law firm of Greenberg Traurig Hoffman Lipoff Rosen & Quentel (hereafter: "the Greenberg Petition") seeking to deny exclusivity to nicotine patch smoking cessation products for OTC use, including Habitrol®.² For the reasons stated herein, FDA should grant NCH three years of market exclusivity when it approves NCH's supplemental NDA for an OTC Habitrol® product and, consequently, must also deny the Greenberg Petition.

I. BACKGROUND

On January 13, 1984, FDA approved the first prescription smoking cessation product containing nicotine, Nicorette®, a chewable gum developed by Merrell Dow, now a part of Hoechst Marion Roussel ("HMR"). Since Nicorette®'s introduction in 1984, FDA has approved several other prescription products, in various dosage forms, containing nicotine and indicated generally to help people quit smoking. In approving the prescription nicotine substitution products, FDA has consistently recognized that each innovator's product required its own full new drug application under § 505(b) of the Federal Food, Drug, and Cosmetic Act ("the Act"),³ and, thus, was a distinctly different product from any other nicotine substitution drug product.⁴

In March 1994, FDA issued a draft guidance on how to demonstrate the safety and effectiveness of nicotine substitution products when used under OTC conditions. A copy of that draft guidance is attached to, and incorporated by reference into, these comments as Exhibit A. Compliance with that draft guidance required that the holders of prescription nicotine substitution products provide detailed safety and effectiveness data to FDA to support the OTC use of their products.

On February 9, 1996, the agency approved an application by SmithKline Beecham Consumer Healthcare ("SmithKline") to "switch" Nicorette® from sale solely as a prescription

² FDA Docket No. 97P-0079.

³ Codified at 21 U.S.C. § 321, *et seq.*

⁴ FDA's handling of each company's nicotine substitution product under separate new drug applications is consistent with the Supreme Court's holding in U.S. v. Generix Drug Corp., 460 U.S. 453 (1983).

November 17, 1999

Page 3

product to OTC marketing.⁵ In conjunction with that approval, FDA awarded SmithKline three years of exclusive marketing pursuant to the Waxman-Hatch Act, as it amended the Act.

The issue of whether FDA could validly grant exclusivity to Nicorette® upon its approval for OTC marketing was the subject of a petition filed by the law firm of McKenna & Cuneo, L.L.P. (hereafter: "The Nicorette® Petition"). The Nicorette® Petition, filed in November 1995 even before the Nicorette® OTC approval, raised numerous objections to any potential grant of exclusivity to Nicorette® relating to its potential Rx-to-OTC switch. In February 1996, shortly after Nicorette®'s approval for OTC marketing, the McKenna firm filed a Petition to Stay any award of exclusivity to the Nicorette® Rx-to-OTC switch.

FDA denied both the Nicorette® Petition and the Petition to Stay by letter dated October 31, 1996, to Gary L. Yingling, Esq. (hereafter: "the Yingling Letter"). The Yingling Letter, in explaining FDA's decision to award three-year exclusivity to the Nicorette® Rx-to-OTC switch applications,⁶ discusses many aspects of FDA's views on the applicability of three-year exclusivity to Rx-to-OTC switches⁷ and, ultimately, determined that the Nicorette® application met the statutory criteria for a three-year exclusivity award.

In the summer of 1996, FDA also approved Rx-to-OTC switches for two other transdermal patch nicotine substitution products – Nicotrol® and Nicoderm® CQ. FDA

⁵ The product was marketed as a prescription product under a joint venture between HMR and SmithKline. HMR apparently transferred the ownership of the underlying NDAs to SmithKline sometime prior to the February 1996 Rx-to-OTC switch approval as the FDA's reference, *Approved Drug Products with Therapeutic Equivalence Determinations*, 14th Edition (1997) (hereafter: "The Orange Book"), names SmithKline as the holder of the NDA under which the OTC switch was approved.

⁶ The Nicorette OTC switch approvals were actually for supplements to the NDA's covering the 2 mg. (N18612) and 4 mg. gums (N20066).

⁷ To the best of our knowledge, FDA's position on three-year exclusivity for Rx-to-OTC switches has not changed since FDA issued the Yingling Letter in October 1996. While we will discuss in greater detail in these comments why the Greenberg Petition should be denied, a straightforward review of the Yingling letter makes clear that the Greenberg Petition does not raise any novel issue of a legal or factual nature that would preclude a grant of exclusivity to Habitrol, assuming that we, as Habitrol's sponsor, can satisfy the statutory language governing exclusivity.

November 17, 1999

Page 4

awarded both products three years of exclusive marketing under the Waxman-Hatch Act.⁸ In March 1997, although FDA had already approved both the Nicotrol® and Nicoderm® CQ switch applications and also had already awarded both products exclusivity,⁹ the Greenberg Petition was filed. That petition asked FDA to deny exclusivity to all nicotine substitution products that sought a switch from Rx to OTC use. The Greenberg Petition has been pending since that time. NCH submits this letter in support of FDA's consistent application of the grant of market exclusivity to those Rx-to-OTC switch products that, like Habitrol®, fulfilled the statutory requirements for an exclusivity award, as discussed in detail below.

In the interim, according to press reports and at least one FDA document¹⁰ – but not yet reflected in the Orange Book – on December 23, 1998, the agency approved the Rx-to-OTC switch application of another nicotine substitution product, Elan's NTS™ (nicotine transdermal system).¹¹ NCH has not learned whether the agency has granted exclusivity to that product.

⁸ The sole explanation in the Orange Book as to why FDA granted exclusivity to the Nicotrol® and Nicoderm® CQ Rx-to-OTC switch NDAs (20165 and 20536) was that they constituted "new products" (indicated in the Orange Book by a "NP" designation). Presumptively, that exclusivity, because it was three years in length, had to have been based on one or more of the following statutory exclusivity clauses: 21 U.S.C. §§ 355(c)(3)(D)(iii), 355(c)(3)(D)(iv), 355(j)(4)(D)(iii), or 355(j)(4)(D)(iv), which all contain identical qualifying language requiring, in summary, that, to get exclusivity, the application must have contained new essential clinical investigations conducted or sponsored by the applicant.

⁹ NCH could not locate evidence of exactly when FDA made the decisions awarding exclusivity to OTC Nicotrol® and Nicoderm®. However, those awards were made at least by January 31, 1997, as both awards are listed in the exclusivity addendum to the 17th Edition of the Orange Book, which contained information current through that date.

¹⁰ March 30, 1999 letter from Dr. Janet Woodcock, Director, FDA Center for Drug Evaluation and Research ("CDER"), to Dr. Sidney Wolfe, Public Citizen, denying a 1992 petition seeking to add a boxed warning to labeling of nicotine patch products. See p. 1.

¹¹ NDA 18863; supplement approved on December 12, 1998. As a prescription product, Elan's product was sold under the trade name, Prostep®, and was distributed by Wyeth-Ayerst Laboratories. We understand that, as an OTC product, the product will be distributed by Perrigo.

November 17, 1999

Page 5

II. THE LEGAL STANDARD FOR THREE-YEAR EXCLUSIVITY AND ITS APPLICATION TO A HABITROL® RX-TO-OTC SWITCH NDA APPROVAL

Before addressing specific issues raised in the Greenberg Petition, we will first review the state of the law relative to three-year exclusivity and discuss why, upon an NDA approval for an Rx-to-OTC switch¹² of Habitrol®, three-year exclusivity must be granted.

A. The Statutory Language

In order to qualify for three-year exclusivity, the Rx-to-OTC switch applications of Nicorette®, Nicotrol® and Nicoderm® CQ each had to separately satisfy the Waxman-Hatch Act's provisions on exclusivity which, in pertinent part, award exclusivity to a new drug application (or a supplement thereto) approved under § 505(b) of the Act that contains:

... reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant.

21 U.S.C. § 355(c)(3)(iii) and (iv).

The statute provides no further discussion of what Congress meant by the precise language of the three-year exclusivity provision, particularly the key terms "new," "clinical investigations," "essential to the approval of the application" and "conducted or sponsored by the applicant." Recognizing that this and other parts of the statutory language of the Waxman-Hatch Act would require further development through rule-making, Congress directed FDA to promulgate regulations to implement the 1984 law. FDA implemented the exclusivity parts of the statute in October 1994.¹³ Rather than discuss FDA's regulations in their abstract, these comments will establish that, when applied to the Habitrol® Rx-to-OTC switch application, FDA should grant exclusivity to that switch. Thus, FDA also must deny the Greenberg Petition.

¹² As will be discussed in greater detail later in these comments, because NCH has proven that its OTC Habitrol® is effective for an eight-week course of treatment as opposed to the ten weeks approved for Habitrol® as a prescription product, this NDA supplement, in the agency's view, technically may not be an Rx-to-OTC "switch" at all. For convenience's sake, NCH nonetheless will refer to this supplement as involving an Rx-to-OTC switch.

¹³ 59 F.R. 50337 (October 3, 1994); 21 C.F.R. § 314.108.

November 17, 1999

Page 6

B. Because NCH Sponsored The New Clinical Investigation Essential to the Approval of a Switch from Rx-to-OTC Labeling, Habitrol® Is Entitled to Three Years of Exclusivity

The Greenberg Petition concedes, at page 18, that:

...[E]xclusivity for Habitrol® should rest solely on whether Ciba Self Medication [now NCH], the sponsor of the OTC switch NDA (#20076-S006) for Habitrol®, performed its own essential and new clinical investigations.

We agree. Indeed, this statutory requirement was applied by FDA to the Rx-to-OTC switch applications of Nicorette®, Nicotrol®, and Nicoderm® CQ. Thus, because NCH has performed the statutorily required new essential clinical investigation to support the Habitrol® switch (study CCP94-002), it should be awarded three years of exclusivity.

1. The 1994 Guidance Requires New Clinical Investigations to Justify Many Different Aspects of OTC Nicotine Substitution Products. Including Proving the Comparable Efficacy of the OTC Product to the Original Prescription Formulation

On March 1, 1994, the agency issued a draft guidance entitled "Requirements for Approving OTC Nicotine Substitution Products."¹⁴ In that guidance, FDA stated:

...[T]he basic presumption which needs to be established by substantial evidence derived from adequate and well controlled studies is that adequate directions can be written for safe and effective use of the product by consumers.

Id. at 1.

The guidance continued by saying that those adequate directions for OTC use needed to accomplish, *inter alia*, a showing that the OTC nicotine substitution product¹⁵ could "*achieve comparable efficacy to 'average' treatment with prescription products.*" Id. (Emphasis added.)

¹⁴ Issued by the Pilot Drug Evaluation Staff & Office of OTC Drug Evaluation, CDER, FDA.

The guidance document also articulated other factors a sponsor would have to show to secure approval of an Rx-to-OTC switch of nicotine patches. These included demonstrating that (1) consumers could self-select themselves for treatment; (2) consumers could identify and deal with emergent treatment signs and symptoms; and (3) the product was resistant to misuse, abuse or chronic use for other indications that might pose a risk to the public. The agency made clear that, to satisfy the guidance, would require more than one type of study:

Previous experience has shown that no single trial can effectively meet such varied requirements and therefore they will be best met by selecting appropriate patient populations for their differing objectives.

Id. at 1.

Thus, FDA set a fairly high "bar" for an Rx-to-OTC switch of a nicotine substitution product and anticipated that several different types of studies might be required to justify a switch. The question relative to NCH's entitlement of exclusivity is whether any such study conducted or sponsored by NCH meets the statutory/regulatory requirements of "essential new clinical investigations." As mentioned, study CCP94-002 does.

2. NCH Conducted a New Essential Clinical Investigation That Compared the Efficacy of Habitrol® When Used Under OTC Conditions Against Its Use Under Prescription Dispensing and, Thus, Is Entitled to Exclusivity

a. *The Rx-to-OTC Comparable Efficacy Study Is A Clinical Investigation*

FDA regulations define "clinical investigation," at 21 C.F.R. § 314.108(a), as:

[A]ny experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects.

(Footnote cont'd from previous page.)

¹⁵ The guidance applies to all nicotine substitution products proposed for switching from Rx to OTC status, regardless of dosage form. For convenience's sake, NCH hereafter will refer to transdermal nicotine substitution products as "nicotine patch(es)."

Put simply, if, in the course of an experiment, human subjects use the drug, that experiment meets the definition of a clinical study. Thus, it is clear that OTC usage studies are clinical investigations for purposes of Waxman-Hatch Act three-year exclusivity.¹⁶

In this case, NCH performed an OTC usage study to meet FDA's 1994 guidance requirement that it compare efficacy under OTC conditions to that achieved via prescription dispensing. This Habitrol® OTC usage study is a "clinical investigation" for purposes of the Waxman-Hatch Act. Indeed, the Yingling Letter, in rejecting an assertion that OTC usage studies were comparable bioavailability studies, recognized explicitly that OTC actual use studies are clinical investigations for Waxman-Hatch purposes:

Although clinical investigations were conducted by the sponsor to show, among other things, that Nicorette's efficacy when used by a consumer without the intervention of a physician is comparable to its efficacy under average prescription use, it was clearly not the purpose of these investigations to show comparable bioavailability. Rather, the purpose was to show that differences in patient populations and the way the product is used OTC (i.e., without the intervention of a physician) would not affect Nicorette's efficacy relative to prescription use.

Yingling Letter at 5. Similarly, the Habitrol® efficacy study, which investigated the actual use of Habitrol® in an OTC setting, is a clinical investigation.

b. The Rx-to-OTC Comparable Efficacy Study Is A New Investigation

For Waxman-Hatch exclusivity purposes, FDA defines "new" relative to clinical investigations in a non-temporal manner. A new study is not one done recently in time. Rather, under 21 C.F.R. § 314.108(a), an investigation is new if it is:

¹⁶ See Yingling Letter, at 4-5. See also, CDER Manual of Policy and Procedure (MAPP) #6532.1, at page 2, which describes an "OTC drug actual use study" as "a controlled experiment in which a prescription drug or an unapproved new drug is used by subjects under OTC-like conditions." Because the drug is actually used by subjects, an OTC drug actual use study clearly meets the regulatory definition of a clinical investigation established in 21 C.F.R. § 314.108(a).

November 17, 1999

Page 9

... An investigation in humans the results of which have not been relied upon by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.

In lay terms, if FDA has not used a study before to support an approval, it is new.¹⁷ NCH's CCP94-002 satisfies the "new" requirement.

- (1) **The efficacy study has never been used to show substantial evidence of effectiveness of any other previously approved drug product.**

Given the fact that Habitrol®, at this writing, remains available solely by prescription, it is axiomatic that a study such as CCP94-002 done by NCH on Habitrol® that explores its use OTC has not been used to show substantial evidence of any other approved drug product. In addition, NCH has never submitted CCP94-002 in support of any other drug product or in any filing prior to this supplement.

- (2) **The efficacy study does not duplicate the results of any investigation relied on previously by the agency to approve any other drug.**

It also is axiomatic that the comparable efficacy studies of Habitrol® in both OTC and prescription use, performed as CCP94-002, did NOT duplicate the results of any investigation relied on previously by FDA. This conclusion is obvious because no other study exists, other than those in this yet-to-be approved Habitrol® Rx-to-OTC switch supplemental new drug application file, that compare Habitrol® as an OTC product versus Habitrol® as a prescription drug. Thus, the study conducted by NCH is a new investigation.

¹⁷ The first instance in which the agency articulated this view was in finding that a study done in 1969 was "new" for purposes of granting exclusivity to a supplemental NDA approved in 1986 for a new indication for Persantine® (dipyridamole). See FDA Docket 87P-0118, August 9, 1988 letter of FDA Associate Commissioner for Regulatory Affairs, John M. Taylor, to the law firm of Bass & Ullman.

c. The Rx-to-OTC Comparable Efficacy Study Is An *Essential* Investigation

To be "essential to approval" under 21 C.F.R. § 314.108(a), means that, "with regard to an investigation, that there are no other data available that could support approval of the application." In applying this definition, FDA has consistently taken the approach that, if the application could be fully approved without a particular investigation, then that investigation (that was not needed to secure approval) could not be essential to approval. However, if without the investigation, FDA could NOT approve the application, but could approve it when considering the investigation, the investigation must be essential.

Applying this standard to the real example of the Rx-to-OTC switch of Nicorette®, the agency made clear in The Yingling Letter that comparable OTC vs. Rx studies were essential to approval:

The agency disagrees with your statement that the studies conducted by the Nicorette sponsor were not essential to the approval of the Nicorette Rx to OTC switch supplements. *Essential to approval* means that there are no other data available that could support approval of the application (21 CFR 314.108.) In determining whether a clinical study is essential to the approval of a supplement, there are two relevant considerations. First, the data generated in the clinical study or studies must be necessary to support the safety or efficacy of the proposed change. Second, there must not be published reports of studies other than those conducted by or sponsored by the applicant, or other information available to the Agency, sufficient for FDA to conclude that the proposed change is safe and effective....

The Agency has determined that the data generated in the clinical studies conducted by the Nicorette sponsor were necessary to support the safety of the drug product for OTC use and to demonstrate that the efficacy of the product was within acceptable parameters. Moreover, these data did not duplicate other data in the NDA or publicly available literature.

Yingling Letter at 5 (emphasis in original).

The studies deemed "essential" by FDA in the Nicorette case are the same type of comparable OTC vs. Rx studies conducted by NCH in support of the Habitrol® Rx-to-OTC switch supplement. Moreover, the Habitrol® study was conducted in response to the 1994

Guidance, which established that proof of comparable efficacy of the product when used OTC relative to its effectiveness as a prescription product was required for approval. Thus, it is clear that study CCP94-002, which NCH has submitted in this supplement, and which showed Rx-to-OTC comparability, meets the definition of being "essential" because it is necessary to support a conclusion on the efficacy and safety of Habitrol® as an OTC product.

3. The New Essential Clinical Investigation That NCH Conducted Also Supported a Second and Distinct Major Change In the Labeling of Habitrol® -- the Duration of the Course of Therapy -- and, Thus, Is Entitled to Exclusivity

A separate and distinct basis also exists for FDA to grant exclusivity to NCH relative to this supplemental NDA. Specifically, NCH has proven, in its pivotal study CCP94-002, that Habitrol® is effective as an OTC product when used for a duration of eight weeks. In contrast, the approved prescription labeling requires the patient to continue the use of Habitrol® for ten weeks. This change in duration of use alone, when supported by a new essential clinical investigation, warrants a grant of three-year exclusivity by FDA.

There can be little doubt that changing the duration of use of a prescription product when switching to OTC status is a significant change. Indeed, where there is a duration of use change, FDA has suggested that an "Rx-to-OTC switch" has not even occurred. Rather, the "switched" product there, in the agency's view, constitutes the "initial marketing of an OTC product" because a duration in use difference renders the product distinctly different from its prescription ancestor. FDA's position on this issue is clear from its Manual of Policy and Procedure (MAPP) #6020.5, which governs internal agency procedures for reviewing Rx-to-OTC switches. The MAPP contains the following illustrative definitions that show that changing the duration of use of a prescription product in securing OTC marketing creates a totally new product:

Rx to OTC Switch. This refers only to OTC marketing of a product that was once a prescription product for the same indication, strength, dose, duration of use, dosage form, population, and route of administration.

Initial Marketing of a Drug Product OTC. This category of product could be one of two types: (1) OTC marketing of a product that was never previously marketed as a prescription drug product or (2) OTC marketing of a product in a strength, dose, route of administration, duration of use, population, indication, or dosage form different from ones previously approved for prescription use.

FDA MAPP #6020.5 at p. 2. (Emphasis added.)

Given that no other OTC (or Rx) nicotine patch product is approved for an eight-week duration of use and that NCH conducted the pivotal study CCP94-002 that proved the safety and effectiveness of Habitrol® for that shorter duration of use, NCH has conducted a new, essential, clinical investigation to support a major change in the Habitrol® product that has, until now, been marketed as a prescription only product. NCH, thus, also qualifies for exclusivity under the Waxman-Hatch Act because this supplement contains a new essential clinical investigation that proves Habitrol® can be used under OTC conditions for a shorter duration of use than currently approved for prescription dispensing.¹⁸

C. In Summary, the Habitrol® Rx-to-OTC Switch Investigation Supports Not One, But Two Major Changes in the Conditions of Use for Habitrol®, Each One of Which Alone Would Warrant Exclusivity

As the Greenberg Petition conceded, exclusivity for Habitrol® should rest "solely on whether [NCH] the sponsor of the OTC switch ... for Habitrol®, performed its own essential and new clinical investigations." As shown, NCH's pivotal new clinical investigation, CCP 94-002, is essential to the approval of two major changes in Habitrol®'s conditions for use.

First, CCP94-002 proved, for the first time, that the effectiveness of OTC Habitrol® compared favorably to that of Habitrol® when used as a prescription product and that its use could be properly administered by a patient without the instruction of a physician. That major accomplishment alone justifies an award of exclusivity.

Second, Habitrol® study CCP94-002 demonstrated comparable efficacy, under OTC conditions, in a shorter course of treatment than that which was approved for the prescription version of Habitrol®.

The statute dictates, therefore, that upon approval of its supplement to switch Habitrol®, NCH should be awarded three years of market exclusivity. Such a grant is consistent with the

¹⁸ Given the health concerns associated with nicotine intake from any source, this shorter use period also represents a significant potential health benefit for both Habitrol® users and any other nicotine patch user seeking to minimize their intake of nicotine, but still participate in a smoking cessation program involving a nicotine replacement.

law, fact, and sound public policy.¹⁹

III. COMMENTS ON THE GREENBERG PETITION

The Greenberg Petition raises an array of points to try to support its view that FDA should deny exclusivity to the applications that supported Rx-to-OTC switches of Nicotrol® and Nicoderm® CQ, and any pending applications that might support switching Habitrol®, and other nicotine patch products. In our view, these points, whether taken individually or collectively, fail to establish that "switched" nicotine replacement products are not entitled to exclusivity. These comments, thus, will rebut the Greenberg Petition from both a general perspective and, where appropriate, by specific critiques of particular arguments asserted in the Greenberg Petition that are unsupported by law, fact, or both.

A. General Observations

The Greenberg Petition's global defects stem from at least two faulty premises. First, because the petition seeks to bar exclusivity for any already-approved Rx nicotine patch product that might switch to OTC availability, the petition attempts to treat all nicotine patch products as if they were a homogeneous "class" of products to which general principles of safety and effectiveness can be applied. In doing so, the Greenberg Petition applies sweeping conclusions to products of diverse companies without regard to the fact that, whether viewed from a pharmacological, physical, or legal perspective, all are distinctly different products.²⁰

¹⁹ OTC availability of drugs previously available only by prescription serves the public health by reducing the overall cost of medical care (e.g., via cutting doctor bills), possibly by as much as \$20 billion each year. See "Now Available Without a Prescription," FDA Consumer, November 1996. Thus, having incentives such as market exclusivity available to encourage switches is clearly in the public interest.

²⁰ A "class" view of OTC products, where general safety and efficacy conclusions are sought relative to all similarly-situated products, may be appropriate for products such as those that went through FDA's OTC Drug Review, but has no sound legal or public policy foundation in dealing with products originally marketed as prescription products when they are proposed for switching to OTC availability through the NDA process. See also, Pfizer v. FDA, 753 F. Supp. 171 (D.Md. 1990), which approvingly quoted USV Pharmaceutical Corp. v. Weinberger, 412 U.S. 655, 664 (1973) in discussing the definition of "drug product:"

It is true that an NDA covers a particular product or product that it names and that [21 U.S.C. § 355] when applied to an NDA is personal to the manufacturer

(Footnote cont'd on next page.)

November 17, 1999
Page 14

The Greenberg Petition thus ignores not only logic, but established legal precedent that a drug product is not just determined by its active ingredient, but also with respect to all other aspects of the product and its formulation including, but not limited to, route of administration, dosage form, delivery system, labeling, duration of use, etc.²¹

Second, by failing to regard the already-approved products as each being a distinctive product, the Greenberg Petition never examined – on a case-by-case basis – whether an award of three-year exclusivity might be valid in any one individual product's circumstances. However, FDA, upon approving both Nicotrol® and Nicoderm® CQ, concluded that each of those products was entitled to three-year exclusivity. While the record of FDA's decision in awarding these products exclusivity was not available at the time these comments were prepared, the only logical conclusion is that FDA must have recognized that, on its individual merits, each product separately met the criteria for exclusivity under the Waxman-Hatch Act.

(Footnote cont'd from previous page.)

who files it. Section [355], in other words, addresses itself to drugs as individual products.

Pfizer, at 178.

²¹ Generix, supra. FDA recently reiterated this principle in the context of "180-day" or "ANDA" exclusivity under the Waxman-Hatch Act [21 U.S.C. § 355(j)(4)(D)(iv)]. On December 4, 1998, in a letter from FDA CDER Director, Janet Woodcock, the agency rejected a Torpharm petition that had argued that Novopharm was not entitled to ANDA exclusivity on a 75mg. ranitidine product because a different strength of ranitidine had already enjoyed 180-day exclusivity. Torpharm had petitioned that, because the statute used the term "drug" in the ANDA exclusivity clause, once there was a first commercial marketing of any ranitidine product – even if under a different strength – no subsequent ranitidine approval could qualify for ANDA exclusivity. In denying Torpharm's petition, FDA made clear that:

...FDA does not define drug product to mean active ingredient. Rather, it "means a finished dosage form, for example, tablet, capsule, or solution that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients." [quoting 21 CFR 314.3(b). Woodcock letter, at pages 2-3.

The agency's view was recently upheld by the federal courts. See June 16, 1999 Memorandum Opinion and Order in Apotex, Inc. v. Shalala, Civ. No. 99-729, U.S. District Court for the District of Columbia.

And, as the Yingling Letter makes clear, many unique aspects, all consistent with the legal requirements for exclusivity, existed in the Nicorette® Rx-to-OTC switch application that provided grounds for FDA to grant exclusivity to Nicorette®'s switch. FDA should continue that same case-by-case analysis relative to the Rx-to-OTC switch of Habitrol®.

B. Specific Comments

In addition to its fundamental global flaws, the Greenberg Petition also contains a number of specific assertions that we believe do not pass reasoned scrutiny.

1. The Safety Of OTC Nicotine Patches in General or Habitrol® Specifically Has Not Yet Been Shown on Such a General Basis as to Preclude the Needs for Clinical Investigations For Nicotine Patch Rx-to-OTC Switches

The Greenberg Petition contains a lengthy argument that sponsors of prescription nicotine patch products no longer need prove, in conjunction with their Rx-to-OTC switch applications, that the OTC use of their products is safe. The petition contends that the necessity to affirmatively perform any safety studies has been obviated since Nicorette® was approved for OTC sale in February 1996 because so much information now exists in the published literature on nicotine and its safe use, particularly relative to smoking as a source of nicotine. In other words, the Greenberg Petition asserts that proof of safety via clinical investigations would be duplicative and unnecessary for any nicotine substitution product.²² The petition's reasoning is flawed both generally and particularly.

- a. **Contrary To What The Greenberg Petition Suggests, Proof Of Safety Of One OTC Nicotine Substitution Product Does Not Automatically Extend To Other Nicotine Substitution Products.**

Each of the nicotine patch products is a unique product, all listed separately in FDA's Orange Book, even when they all were available solely by prescription. Thus, while the data in one company's OTC switch NDA on safety may be helpful for FDA to reach a general view that nicotine patch products are safe when used OTC, the other company's data do not address the specific question of whether the individual product proposed for switching may be safely used

²² See Greenberg Petition, pages 7 to 11.

under OTC conditions.²³ That question can only be explored, as was done with Habitrol® in accordance with the 1994 Guidance, by comparing the OTC version of a product against its use as a prescription product.

b. The Greenberg Petition Fails to "Prove" The Safety Of Nicotine Substitution Products.

The Greenberg Petition's safety discussion deals extensively with nicotine withdrawal and a smoker's ability to deal with nicotine toxicity. Because smokers allegedly can deal with those challenges, the Greenberg Petition concludes that the safety of nicotine patches has been proven to the point where additional clinical investigations are not needed to show how nicotine patch users can manage adverse events.²⁴

However, all the data cited to support the proposition is based on management by current smokers of nicotine intake. It is not based on how nicotine patch users themselves can manage adverse events. Relying purely on data as to how smokers manage adverse events when considering the safety of smoking cessation products compares two distinctly different sample populations. For there is a plain and fundamental difference between smokers and patch users; namely, the patch user is NOT to be smoking if he/she is following the product's directions for use. Thus, any data generated relating to how smokers manage adverse events does not correlate to how patch users manage adverse effects, as they are patently different subject populations.

The Greenberg Petition's analysis also ignores many of the other objectives that the 1994 guidance required be proven in connection with an Rx-to-OTC switch, such as whether the OTC directions for use would be adequate to permit the patient to self-select for treatment or identify and deal with treatment emergent signs and symptoms. In this respect, it is important to note that the potential "signs and symptoms" associated with nicotine patch use include considerations other than just managing nicotine intake. Indeed, the prescription labeling for Habitrol®

²³ FDA's handling of exclusivity decisions on the various nicotine patches as prescription drugs was consistent with the view expressed herein that the agency must review each manufacturer's product's entitlement to exclusivity separately. In approving both the prescription Nicoderm® CQ (then called simply "Nicoderm") and the prescription Habitrol® products, FDA awarded each NDA, upon approval, three years of market exclusivity. If FDA were to accept the ill-founded "logic" of the Greenberg Petition, it arguably would have had to have denied exclusivity to prescription Habitrol® simply because Habitrol® received its approval about three weeks after the Nicoderm® prescription approval in 1992.

²⁴ The Greenberg Petition, at pages 8-9.

November 17, 1999

Page 17

includes at least seven bolded headings under "Precautions," ranging from "Allergic Reactions" to "Peptic Ulcer Disease." Thus, even if the Greenberg Petition arguably had proven that quitters can manage nicotine toxicity, that would address only one small aspect of whether Habitrol® can be used safely as an OTC drug.

We do not suggest that studies done on other nicotine patches do not provide helpful collateral information for FDA as to the general safety of the class of products known as nicotine patches. But, to justify a switch of Habitrol® to OTC status, FDA required that NCH show that the frequency of adverse events linked to Habitrol® itself did not increase to any significant degree under OTC conditions when the intervention of a physician is removed. Showing the safety of OTC vs. Rx use of Habitrol®, *a fortiori*, could only have been done in a clinical investigation to be found in the Habitrol® switch NDA because, before being studied under OTC conditions by NCH, an OTC version of Habitrol® simply did not exist.^{25 26} Indeed, the only OTC "version" that will have been "available" for study before FDA approves an Rx-to-OTC switch of Habitrol® will be that product studied in protocol CCP94-002 by NCH under an IND.

Another major safety point raised in the Greenberg Petition is that the safety of OTC use of nicotine patches is proven by five years of use as a prescription product because, in "reality," there was no involvement of a physician historically in the use of nicotine patches.²⁷ This argument is unfounded on several points. First, that statement in the Greenberg Petition is nothing greater than a naked conclusion of the author. The Petitioner offers no citation to any

²⁵ The public health basis for insisting that the OTC safety and effectiveness of Habitrol® rest on data generated from clinical investigations specifically performed on Habitrol® itself is heightened by another factor -- the fact that FDA has already approved generic equivalents to the Rx versions of Habitrol® (ANDAs # 74615, 74611, and 74612, held by Sano Corporation, approved October 20, 1997. See Orange Book, 19th Ed., at 3-245). Thus, accepting the Petitioner's argument to deny exclusivity to Habitrol® would mean that, after Habitrol®'s OTC approval, presumably no known legal impediment would exist to block FDA from approving a labeling change for Sano's product to change to OTC status, as the bioequivalence of the Sano product was already proven to FDA's satisfaction when FDA approved Sano's prescription ANDA.

²⁶ Contrary to the Greenberg Petition, the safety of OTC Habitrol® could not be proven solely by the data cited in the Greenberg Petition. Rather, FDA insisted that NCH prove that OTC Habitrol® could be used safely compared to the Rx Habitrol®. NCH did so by means of clinical investigations.

²⁷ *Id.*, at 10. Petitioner makes this argument to help justify its conclusion that proof of OTC safety has already been proven without the need for any additional studies by NCH.

authority to back its claim that there was no physician intervention while Habitrol® -- or any other nicotine product -- was being dispensed as a prescription product.

Thus, Petitioner's argument that FDA should be able to extrapolate prescription use of nicotine patches to reach a decision on granting OTC uses rests, in a major respect, on Petitioner's unproven assertion that there was no doctor intervention while these products were being used Rx. This premise also makes no sense for an Rx-to-OTC switch because it ignores that one of the basic issues that any Rx nicotine patch NDA holder had to prove to switch to OTC status was to assess whether the lay person can safely diagnose and use that product on an OTC basis.²⁸

In addition, to say that there was no doctor intervention in prescription drug use ignores a fundamental aspect of prescription drug use -- that no patient can legally gain access to a prescription drug without first securing a doctor's prescription. As the use of a prescription product thus always legally depends on the intervention of a doctor, extrapolation of allegedly safe Rx use to prove safe diagnosis and use of an OTC product in the absence of a doctor's intervention defies logic.

2. The Effectiveness of Nicotine Patches in General or Habitrol® Specifically for OTC Use Has Not Yet Been Proven So as to Preclude the Need for Clinical Investigations For Nicotine Patch Rx-to-OTC Switches

Curiously, the Greenberg Petition devotes little attention to showing that there is no need for clinical investigations into the *effectiveness* of nicotine patch Rx-to-OTC switches in general or Habitrol® specifically. The reason for this scanty treatment of a key issue in the question of whether a Habitrol® Rx-to-OTC switch should get three-year exclusivity is simple: no publicly available data exist, outside the Habitrol® Rx-to-OTC switch supplemental NDA, to *prove*, with substantial evidence, the effectiveness of the switch of Habitrol® (or any other nicotine patch product) from Rx to OTC availability.

Indeed, the Greenberg Petition offers *no* evidence of any available clinical investigations that compared the effectiveness of any nicotine patch used under prescription conditions against that same product's effectiveness when used OTC. Rather, as sole support for its assertion that the efficacy of OTC nicotine patches has been proven, the Greenberg Petition offers a meta-

²⁸ 1994 Guidance, at 1-2.

November 17, 1999

Page 19

analysis²⁹ that found nicotine patches were effective over placebo. While that information may be helpful to FDA in assessing the general effectiveness of nicotine patches, it is irrelevant to the specific effectiveness question that the 1994 guidance asked, and NCH has answered, relative to the Rx-to-OTC switch of Habitrol®.

The Greenberg Petition's discussion of the Fiore meta-analysis is also misleading, as the petition contends that the meta-analysis "found that nicotine patches were effective over placebo without regard to professional supervision."³⁰ We could find no statement in the Fiore study report that substantiates this bald assertion from the Greenberg Petition. In fact, a review of that study report makes clear that it did not opine, in any way, on the effectiveness of nicotine patches in the absence of professional supervision.

First, one of the criteria for inclusion in the meta-analysis was that the study involved some level of counseling. Second, there are numerous statements in the published Fiore report that make clear that no conclusions were reached as to the effectiveness of nicotine patches in the total absence of professional supervision (e.g., in an OTC setting). Rather, the Fiore report carefully pointed out that intensity of counseling did not appear to have any impact on the effectiveness of patch use vs. placebo:

It is clear from the results of this meta-analysis that the efficacy of the nicotine patch, relative to the placebo patch, was essentially unrelated to adjuvant intensity.³¹ [Emphasis added.]

At best, therefore, the Fiore meta-analysis supports the use of nicotine patches with minimal counseling. It clearly left open the question of how effective nicotine patches would be without any counseling such as in OTC use:

Although intensive adjuvant counseling appears to improve overall rates of smoking cessation, such counseling [i.e., intensive] is not critical to ensuring acceptable levels of efficacy. This suggests

²⁹ Fiore, MC, Smith, SS, Jorenby, DE, Baker, TB, "The Effectiveness of the Nicotine Patch for Smoking Cessation: A Meta-Analysis," JAMA, 1994; 271:1940-47. A meta-analysis is, itself, not a clinical investigation, but a composite analysis of the results from other studies.

³⁰ Greenberg Petition, at 11.

³¹ Fiore, at 1945.

that a stepped-care approach may be appropriate for smoking similar to that used for hyperlipidemia and hypertension. In such an approach, the patch might be accompanied by little or no counseling in its initial use and with increasing amounts of counseling in re-treatments.³² [Emphasis added.]

As to Habitrol®, NCH has answered the question raised by Fiore positively by doing a new essential clinical investigation showing that a nicotine patch product used OTC has comparable efficacy to the same patch used under prescription conditions. Thus, NCH has earned exclusivity under the Waxman-Hatch Act.³³

3. FDA's "Umbrella Policy" on Exclusivity Should Not Be Disturbed

- a. Because NCH is separately entitled to exclusivity, it need not shelter under the umbrella of any other nicotine patch product's Rx-to-OTC switch exclusivity.

The Greenberg Petition contains a lengthy discussion³⁴ as to why FDA should disregard the "Umbrella Policy" established in its rule making on exclusivity.³⁵ In our view, the Umbrella Policy is not implicated by this situation for several reasons.

³² *Id.*, at 1947.

³³ The Greenberg Petition also contains a lengthy analysis of why the effectiveness studies done by the sponsors of the Rx-to-OTC switches for Nicotrol® and Nicoderm® CQ allegedly were defective. We will not address those analyses in detail because, if the Greenberg Petition is correct in its analyses, and those studies were defective, FDA arguably should not have approved those Rx-to-OTC switches and thus, some of the new studies that the Greenberg Petition contends already proved the effective use of OTC nicotine patches should be stricken (due to their defects) from any analysis of exclusivity for Habitrol®. If we were to accept the Greenberg Petition's analysis of these Nicotrol® and Nicoderm® CQ studies and "throw out" those studies (and, presumably, Greenberg would also rescind the approved Nicotrol® and Nicoderm® CQ Rx-to-OTC switch NDA approvals as well), then there can be absolutely no question that the studies NCH has done to prove that Habitrol® is effective when used OTC are essential. And if Greenberg is wrong, the "success" of the Nicotrol® and Nicoderm® CQ effectiveness studies still should have no bearing on Habitrol®'s OTC effectiveness due to the fact that these products are, both factually and legally, distinctly different drug products from Habitrol®.

³⁴ Greenberg Petition, pp. 18-27.

November 17, 1999

Page 21

First, the policy, by its terms, only can be applied in those rare situations where a change might be desirable to a full NDA where the change itself does not need to be supported by clinical investigations, but still might be important to be implemented promptly and would result in the creation of a new drug product that would not be the same as the product enjoying exclusivity.

An example given in the rule-making was a dosage form change (e.g., tablet to capsule). If that occurred, the new capsule dosage form would be a separate and distinct product under a separate NDA that would not be protected by the exclusivity that covered the prior tablet version of the product. And, if that exclusivity had not yet expired, there existed the possibility that a generic applicant could file an ANDA using the changed drug as the listed product and the holder of the NDA for the changed drug would have lost the benefit of its hard-earned exclusivity. To prevent that hardship and presumably to both encourage innovation and not discourage NDA holders from making desirable changes to products, the Umbrella Policy "shelters" the second product under any exclusivity that its sister NDA still enjoyed.

Thus, in this situation, where clinical investigations were required to support the change from Rx to OTC status, NCH qualifies for a separate and distinct exclusivity for the Rx-to-OTC switch that is the subject of this supplement. Thus, there is no need to apply "umbrella exclusivity" because NCH is entitled to primary exclusivity for the very change being effected in this supplement and does not need the "shelter" of any exclusivity that might be enjoyed by any other nicotine patch product.³⁶

(Footnote cont'd from previous page.)

³⁵ 54 Fed. Reg. 28871, 28897 (July 10, 1989).

³⁶ NCH would assert that, assuming, *arguendo*, if it did need to rely on the exclusivity of another nicotine patch product under the "umbrella policy," any such exclusivity should be extended, if appropriate, under the "pediatric exclusivity" provisions of the FDA Modernization Act of 1997 (Pub. L. No. 105-115, 111 Stat. 2296 (1997), as codified at 21 USC § 355A).

- b. Alternatively, if FDA were to deny NCH exclusivity for the Habitrol® Rx-to-OTC switch on the merits of NCH's supplemental NDA, FDA nonetheless should extend the shelter of the umbrella policy to this supplement upon its approval and grant NCH a period of exclusivity based on the exclusivity granted to the Nicoderm® CQ Rx-to-OTC switch.

In the event that FDA might decide that NCH is not entitled to exclusivity on the basis of the new clinical investigations filed with this supplement, NCH asserts that it should enjoy the shelter of the umbrella policy relative to its Rx-to-OTC switch of Habitrol® and that the application of the umbrella policy would be consistent with law and sound public policy.³⁷

The legal basis for applying the umbrella policy to the Habitrol® Rx-to-OTC switch is articulated in detail in FDA's rule-making documents on exclusivity.³⁸ NCH will not repeat those discussions here, especially as the Greenberg Petition does not offer, in our view, any sound legal argument as to why FDA's construction of the Waxman-Hatch Act -- as reflected in the umbrella policy -- should be overturned.

The application of the umbrella policy to the Habitrol® Rx-to-OTC switch also serves sound public policy interests. As shown, Rx-to-OTC switches clearly serve the public interest by reducing health care costs and increasing patient access to safe and effective drug therapies.³⁹ As such, switches are encouraged whenever feasible. However, denying exclusivity to Habitrol® under the umbrella policy also would be counter to the public interest in two key respects.

First, it would undermine the remaining exclusivity that Nicoderm® CQ enjoys because, if NCH secures approval of its Rx-to-OTC switch supplemental application before the end of the exclusivity period granted to Nicoderm® CQ and NCH does NOT receive any exclusivity, no extant legal or regulatory impediment would exist to prevent Sano Corporation from itself

³⁷ Exclusivity for the Nicotrol® Rx-to-OTC switch expires July 3, 1999. For Nicoderm® CQ, exclusivity expires on August 2, 1999. Both exclusivity periods possibly could be extended under the pediatric exclusivity provision, but NCH was not aware as to whether any such award had been made as of the date of this submission.

³⁸ See note 13, *infra*.

³⁹ See note 19, *infra*.

November 17, 1999

Page 23

promptly securing an approval to switch the labeling status of its already-approved prescription nicotine patch product -- for which Habitrol® is the listed drug -- to OTC status. In that scenario, Sano arguably would be able to enter the OTC nicotine patch market as a generic before the Nicoderm® CQ exclusivity ended. Such a result would clearly negate the exclusivity incentive created in the Waxman-Hatch Act and is exactly why FDA implemented the umbrella policy.

Second, if NCH does not benefit from any exclusivity -- direct or under the umbrella policy -- that would create a scenario where it might be in NCH's best interests to delay final approval of this supplemental application until after the exclusivity for both Nicoderm® and Nicotrol® have expired in order to (a) maintain NCH's current unique position as the sole Rx innovator product in the overall nicotine patch market (both prescription and OTC) and (b) to legally ensure that Sano does not enter the OTC market any earlier than possible by legally "denying" Sano the availability of a listed OTC drug upon which to base a supplemental change to its approved prescription nicotine patch product.⁴⁰ This result, while arguably in NCH's best business interests, would be contrary to the public policy objective of making formerly prescription products available over-the-counter.

FDA can avoid these anomalous results by ensuring that NCH enjoys exclusivity for its Habitrol® Rx-to-OTC switch, either directly, as NCH has shown it is entitled, or under the umbrella policy.

IV. CONCLUSION

For the reasons stated herein, FDA, upon approving NCH's supplemental application seeking permission to market Habitrol® over-the-counter, should grant NCH three years of exclusivity under the Waxman-Hatch Act. Concurrently, FDA should deny the Greenberg Petition. If FDA plans to take any action inconsistent with a grant of exclusivity to NCH, we

⁴⁰ For the sake of this discussion and without admitting its validity, we are assuming that FDA would not require Sano to conduct a new bioequivalence study to support the switch of its Rx nicotine patch product to OTC status once Habitrol® is approved for OTC status. However, as separately discussed in Part II-B-3 of these comments, as NCH has proven that Habitrol is effective as an OTC product via a shortened course of therapy (8 weeks as an OTC vs. 10 weeks as an Rx product), NCH would assert that a new bioequivalence study may be appropriate before FDA may approve an OTC version of the Sano nicotine patch. Any greater discussion of that issue will be reserved for a future filing with the agency, if necessary.

November 17, 1999
Page 24

hereby request a meeting with appropriate agency officials prior to the agency taking any final action.

Sincerely,

A handwritten signature in black ink, appearing to read "David P. Tolman". The signature is stylized and written over a horizontal line.

David P. Tolman

Exhibits:

A - March 1994 Draft Guidance

Cc: F. Huser
P. Kantor
T. Dring
C. FitzPatrick

DRAFT

Requirements for Approving OTC Nicotine Substitution Products Pilot Drug Evaluation Staff & Office of OTC Drug Evaluation Center for Drug Evaluation and Research, FDA

The Food, Drug and Cosmetic Act¹ assumes a drug for use by humans should be available over the counter (OTC) unless it:

- "(A) is a habit-forming drug to which section 502(d)² applies; or
- (B) because of its toxicity or other potentiality for harmful effect, or method of its use, is not safe for use except under the supervision of a practitioner licensed by law to administer the drug; or
- (C) is limited by an approved application under section 505³ to use under the professional supervision of a practitioner licensed by law to administer the drug."

All three of the above exceptions are potentially applicable to a consideration of switching nicotine substitution products from prescription to OTC status or qualifying a nicotine substitution product for OTC use without first having it available as a prescription drug.

General guidance on criteria for qualifying a drug for OTC use or switching a prescription drug to OTC status has been offered by the Non prescription Drug Manufacturers Association⁴, Eileen Leonard⁵, Paula Botstein⁶, Carl Peck⁷ and Michael Weintraub⁸.

In the case of nicotine substitution products, the basic presumption which needs to be established by substantial evidence derived from adequate and well controlled studies is that adequate directions can be written for the safe and effective use of the product by consumers. In addition, since nicotine is addictive and in large doses dangerous, as might occur with accidental ingestion by children or pets, any OTC dosage form should not be "abuseable" and should be "safe" to have around small children.

Based on our current understanding of the treatment of individuals who are addicted to nicotine the adequate directions for use need to accomplish the following:

- (1) Permit patient to self-select themselves for treatment appropriately, i.e., selecting self-treatment or consulting a physician, depending on which is indicated by their medical condition(s).
- (2) Achieve comparable efficacy to "average" treatment with prescription products.
- (3) Permit patients to identify and deal with treatment emergent signs and symptoms while using the product, including selecting appropriate self-treatment or consulting a physician depending on which is indicated by their signs and symptoms.
- (4) In addition the product should be resistant to accidental misuse, deliberate abuse, or chronic use for other indications such that it poses an acceptable risk to the public at large.

Previous experience has shown that no single trial can effectively meet such varied requirements and therefore they will be best met by selecting appropriate patient populations for their differing objectives. Smaller trials focusing on groups of patients likely to include a high percentage of

patients who should seek consultation with their physicians would seem best for testing "self-selection" and appropriate "self-treatment" of emergent signs and symptoms [requirements (1) and (3)]. Assessing abuseability and safety for children and pets [requirement (4)] would ordinarily require different populations. The detection of adverse events occurring at the 1/1000 incidence level [requirement (3)] and detecting the likelihood of chronic use for other indications [requirement (4)] will require one or more large multicenter trial(s). Such larger trial(s) should also have, as a secondary purpose, confirming the findings from the smaller trials which were focused on the other 3 requirements.

The FDA definition of quit has been 28 consecutive days of self-reported abstinence with biologic verification (usually expired carbon monoxide). An initial 1-3 weeks after quit (grace period) has been accepted in most studies, but the particular 4 week period must be specified in advance. Follow-up to 6 mos (continuous abstinence) is required and follow-up to 12 mos is desirable.

It is our opinion that these studies should be conducted under an IND. The FDA's Pilot Drug Evaluation Staff and Office of OTC Drug Evaluation are prepared to review all protocol designed to meet the above requirements prior to the finalization of the protocols to give an opinion on whether or not the protocols will meet their stated objectives. Even though the IND regulations only require a review of protocols for safety, it is our opinion that agreement on the likelihood that a study will achieve its objectives, before a protocol is finalized, is in an applicant's best interest as well as the public interest.

To expedite review of your proposals, send two copies (one to each OTC and Pilot Drug)
Office of OTC Drug Evaluation, HFD-830
301-594-2226, fax 594-2222
7520 Standish Place
Rockville, MD 20855-
attn: Debra Bowen
Pilot Drug Evaluation Staff, HFD-007
301-443-3741, fax 443-7068
5600 Fishers Lane
Rockville, MD 20857
attn: Sharon Schmidt

- ¹ Federal Food, Drug, and Cosmetic Act, as amended, section 503(b)(1).
- ² Section 502(d) lists the substances which must bear the "Warning - May be habit forming" label. The list does not contain nicotine.
- ³ Section 505 describes the New Drug Application (NDA) and Abbreviated New Drug Application (ANDA).
- ⁴ NDMA: Comments to FDA on issues relating to switching prescription drugs to OTC status before the Arthritis Advisory Committee, February 22-23, 1990. [PDES #260]
- ⁵ Leonard E: Approval of new drug products. Comments before the Dermatologic Drugs Advisory Committee, March 23, 1992. [PDES #261]
- ⁶ Bostein P: Switching drugs from prescription to OTC through NDAs. Presentation at the Regulatory Affairs Professional Society Meeting, July 17, 1990. 8 pages. [PDES #262]
- ⁷ Peck CP: Principals of Rx to OTC Switch, Presentation at the Arthritis Advisory Committee, February 22-23, 1990. [PDES #263]
- ⁸ Weinraub M: FDA's Perspective on Switch Today. Presentation to NDMA Conference on Rx-to-OTC Switch, September 15, 1992. [PDES #]

Corollaries

As the development of OTC smoking cessation aids evolves, we will attempt to collect specific guidances in the list of corollaries which follow.

- a - The first step is to develop (or at least describe in some detail) the complete OTC Intervention Package (PACKAGE). This PACKAGE might include one or more elements of advertising, display, outer carton labeling, individual product wrapper, package insert, video or audio support tapes, printed support materials, referral to support programs, access to telephone support, passive follow-up, price, and barriers to perpetual use.
- b - The ethical sponsor will, after approval, provide the same (or better) support (materials, hotline, etc.) which comprised the proven PACKAGE.
- c - The price of the PACKAGE and price of any refills is an important parameter. It probably deserves as much consideration in your development plan as the other features of the final PACKAGE. We expect the ethical sponsor to make a good-faith effort to study the PACKAGE at a price which is not substantially different from the post-approval retail price.
- d - Regular use of prescription medications should probably be an exclusion, i.e., be a condition for which the patient should consult their physician. Although a few medications, e.g., theophylline and tricyclic antidepressants, are of particular concern, it may be simpler to specify "regular use of prescription medication".
- e - The US Consumer Product Safety Commission (CPSC), the agency that regulates child-resistant packaging through the Poison Prevention Packaging Act, requests that you inform them of the proposed product, package, and possible hazards. The CPSC is prohibited from releasing trade secret and other confidential business information. 15 U.S.C. 2055(a). Please begin this process as soon as possible as it usually requires a year or more. The CPSC contact is: Susan Barone, 301-504-0477 or 504-0957, fax 301-504-0124.
- f - In assessing the accuracy of self-selection (requirement # 1) for your PACKAGE, consider separately the two types of error, state the target accuracy, and describe how you will iterate your PACKAGE if necessary, i.e., if you do not reach your target. Such assessment can be economically done in settings which would be enriched with high-risk patients, e.g., a cardiology clinic.

		What Patients Actually Did	
		Treat Self	See their MD
What Patients Should Do	Treat Self	CORRECT	Type 1 Error
	See their MD	Type 2 Error	CORRECT

- g - Some high-risk patients (taking prescription medications, pregnant, recent myocardial infarction) will use the medication once it is available OTC (Type 2 Error) and a study design which follows these patients with minimum intervention will provide important safety data.
- h - You may wish to consider retaining some prescription distribution of your product (based on diagnosis or dosage strength) rather than having your product exclusively OTC.

E

Jun-23-00 12:38P

P.02
OTC# 231

EXCLUSIVITY SUMMARY FOR NDA # 20-076 SUPPL # SE6-011

Trade Name Habitrol

Generic Name Nicotine Transdermal System, 21, 14, and 7mg/day patches

Applicant Name Novartis Consumer Health, Inc.

HFD # 560 (OTC)

Approval Date If Known November 12, 1999

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

I. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES / / NO / /

b) Is it an effectiveness supplement?

YES / / NO / /

If yes, what type? (SE1, SE2, etc.)

SE6

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N.A.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N.A.

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

Received Jun-23-00 10:43am

From-

To-McKenna & Cuneo LLP

Page 02

F-043 1-411 P.03/14

6195955450

From-McKenna & Cuneo LLP

Jun-23-00 01:21pm

d) Did the applicant request exclusivity?

YES / X / NO / ___ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? 3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES / X / NO / ~~___~~ / (Rx-to-OTC Switch)

If yes, NDA # N.A. Drug Name N.A.

Per discussion with Dan Hume

Nicoder m eq has received exclusivity. We need to discuss further whether all of the criteria have been met.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / ___ / NO / X /

*OK
5 - finished memo
2/22/00 JG*

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade)

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / ___ /

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / X / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

NA

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / X /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

N.A. YES / / NO / /

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

CCP 94-001 (Prescription Usage Study)

CIBA 94-002 (Study of Usage Behavior and Smoking Abstinence in Cigarette Smokers)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

It is not clear if previously approved drug products apply to other drug products or to this drug product. Please contact me to discuss. CD 2/25/00

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

(same as #2c)

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 30,829 YES / X / ! NO / / Explain: Done by Ciba which later became Novartis

See attached explanation from Novartis

Investigation #2

IND # 30,829 YES / X / ! NO / / Explain: Done by Ciba which later became Novartis

See attached explanation from Novartis

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? N.A. (Owner of IND)

Investigation #1

YES / / Explain ! NO / / Explain

Investigation #2

YES / / Explain ! NO / / Explain

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / / NO / X /

If yes, explain: _____

Robert Merritt 2/2/00
Signature Date
Title: Regulatory Project Manager, HFD-560

[Signature] 2/18/00
Signature of Office Date
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

habxc:for

F

Jun-23-00 12:41P

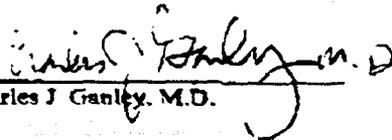
P. 10

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: 2/22/00
From: Director, Division of Over-the-Counter Drug Products
Subject: Exclusivity for Habitrol (NDA #20-076, Supplement #SE6-011)
To: Mary Ann Holovac, HFD-93

This memo is written to clarify a response on form OGD-011347¹ for NDA #20-076, supplement #SE6-011. Under Part I, question #2 asks "Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?" I spoke to Don Hare in the Office of Generic Drugs on 2/17/00 about this and he believed that question #2 should be answered "Yes" because Nicoderm CQ was approved for OTC use previously. Both Nicoderm CQ and Habitrol are transdermal delivery systems containing 7, 14 and 21 mg of nicotine. There are slight differences in the directions for use (i.e. dosing schedule). It is unclear whether these differences are of a magnitude that they would be construed as being the same or different. You will need to make this assessment based on the precedent you have set in the past. The labels for Habitrol and Nicoderm CQ are attached for comparison.


Charles J. Ganley, M.D.

cc: Division File
HFD-560/ganley/katz
NDA #20-076 file

Attachments:
Nicoderm CQ and Habitrol 7 mg labels

Exclusivity Summary

Received Jun-23-00 10:43am

From-

To-McKenna & Cuneo LLP

Page 10

F-043 P. 11/14 T-411

6195955450

FROM-McKenna & Cuneo LLP

Jun-23-00 01:23pm

2/11/00 ps's's part

NICODERM.[®] CO.

nicotine transdermal system
STOP SMOKING AID
14 Patches (Two Week Supply)

- Nicotine stays in the blood under 16 years of age.
- Proof of age is required.
- Not for sale in vending machines or from any source where proof of age cannot be verified.

Manufactured by ALZA Corporation,
Mountain View, CA 94039 for
SmithKline Beecham
Consumer Healthcare, L.P.
Parsippany, NJ 07054.
Made in the U.S.A.
© 2000 SmithKline Beecham

Mr. Dalton CD and Joyce, d/b/a, CD and
Joyce, d/b/a, personal on design, design,
and oral face dress design are
trademarks owned by or licensed to
SmithKline Beecham.

U.S. Patches Numbers:
5.0mg/16h 5.0mg/24h 5.0mg/7d
5.0mg/12h 5.0mg/18h 5.0mg/21d

Drug Facts

Active ingredient (in each patch) Nicotine, 2 mg delivered over 24 hours. **Purpose** Stop smoking aid

Use reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings

- Do not use if you continue to smoke, chew tobacco, use snuff, or use a nicotine gum or other nicotine containing product.
- Ask a doctor before use if you have:
 - heart disease, recent heart attack or irregular heartbeat. Nicotine can increase your heart rate.
 - high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
 - an allergy to adhesive tape or have skin problems because you are more likely to get rashes.
- Ask a doctor or pharmacist before use if you are:
 - using a non-nicotine stop smoking drug.
 - taking a prescription medicine for depression or asthma. Your prescription dose may need to be adjusted when using this product.
- Do not smoke or drink alcohol while wearing the patch. The nicotine in your skin will still be entering your blood stream for several hours after you take off the patch.
- If you have mild dizziness or one or more sleep disturbances, remove the patch at bedtime.

Stop use and ask a doctor if:

- skin redness caused by the patch does not go away after four days or if your skin cracks, or you get a rash.
 - irregular heartbeat or palpitations occur.
 - you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, weakness and rapid heartbeat.
- If pregnant or breast feeding, ask a health professional before use. Nicotine can decrease your baby's heart rate. Try to stop smoking without the nicotine patch. Used together, have enough nicotine to protect children and pets. If swallowed, get medical help or contact a Poison Control Center right away. Dispose of the used patches by taking sticky ends together and placing in disposal tray in the box.

Directions

- If you are under 18 years of age, ask a doctor before use.
- Before using this product, read the enclosed users guide for complete directions and other information.
- Stop smoking completely when you begin using the patch.
- If you smoke more than 10 cigarettes per day, use according to the following 10 week schedule:

STEP 1	STEP 2	STEP 3
14 mg/16h patch daily Weeks 1-2	14 mg/24h patch daily Weeks 3-4	7 mg/24h patch daily Weeks 5-10

- If you smoke 10 or less cigarettes per day, do not use STEP 1 (14 mg) for 2 weeks, then STEP 2 (7 mg) for 2 weeks and then STEP 3.
- Steps 2 and 3 allow you to gradually reduce your level of nicotine. Completing the full program will increase your chances of quitting successfully.
- Apply one new patch every 24 hours on skin that is dry, clean and hairless.
- Remove backing from patch and immediately press onto skin. Hold for 10 seconds.
- Wash hands after applying or removing patch. Throw away the patch in the enclosed disposal tray. See enclosed user's guide for safety and handling.
- You may wear the patch for 16 or 24 hours.
- If you have mild dizziness or other sleep disturbances, you may remove the patch at bedtime and apply a new one in the morning.
- The used patch should be removed and a new one applied to a different skin site at the same time each day.
- Do not wear more than one patch at a time.
- Do not use the patch in hot or dry air or after a shower.
- Do not leave patch on for more than 24 hours because it may irritate your skin and become stronger after 24 hours.
- Stop using the patch at the end of 10 weeks. If you applied with STEP 2, stop using the patch at the end of 8 weeks. If you still feel the need to use the patch talk to your doctor.

Other information (see also 20 mg/24h (8.7 mg))

Inactive ingredients include vinyl acetate copolymer, polyacrylate and high density polyethylene between clear polyester patches.

Questions or comments? call 1-800-4-A-ALZA, ext. 2222 (9:00 a.m. - 4:30 p.m. EST)

Read carton and enclosed User's Guide before using this product. Keep the carton and User's Guide. They contain important information.



STOP SMOKING AID

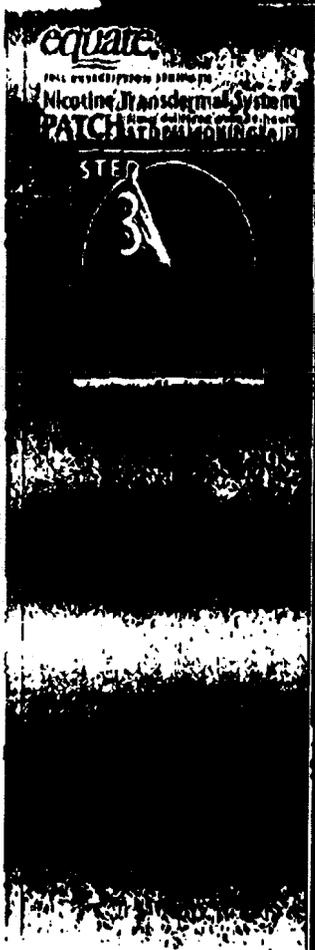
10 WEEKS: YOUR SUCCESS IN QUITTING:

- 1 You must be motivated to quit
 - 2 Complete the full treatment program, applying a new patch every day.
 - 3 Use with a support program as described in the enclosed User's Guide.
- For your family's protection, Nicoderm CD patches are supplied in child resistant pouches. Do not use if individual pouch is damaged or open.
- *SmithKline Beecham provides an educational grant to the American Cancer Society for stop smoking education and cancer-related research in return for the use of their seal.

NO COPY IN THIS AREA FOR IMPRINTING LOT & EXP DATE (1+3/4" X 1+1/4") MIN 1/8" FROM SCORE



- TO INCREASE YOUR SUCCESS IN QUITTING:**
1. You must be motivated to quit.
 2. Use one patch daily according to directions.
 3. Complete the full treatment program.



The use of this product is covered by
U.S. Patent No. 4,597,961 and
5,834,011

Distributed by: NCI, Inc.
Summit, NJ 07901-1312
©1999

Drug Facts	
Active ingredient (in each patch) Nicotine, 7 mg delivered over 24 hours.	Purpose Stop smoking (quit)
Use reduces withdrawal symptoms, including craving, irritability and mood swings.	
Warnings Do not use	
<ul style="list-style-type: none"> • if you continue to smoke, chew tobacco, use snuff, use nicotine gum, or use nicotine patch or other nicotine containing products • Ask a doctor before use if you have: <ul style="list-style-type: none"> • heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate. • high blood pressure not controlled with medication. Nicotine can increase your blood pressure. • an allergy to adhesive tape or have skin problems, because you are more likely to get rashes. • Ask a doctor or pharmacist before use if you are: <ul style="list-style-type: none"> • using a new nicotine stop smoking drug. • taking a prescription medicine for depression or anxiety. Your prescription dose may need to be adjusted. 	
When taking this product	
<ul style="list-style-type: none"> • do not smoke even when not wearing the patch. The nicotine in your skin will still be entering your bloodstream for several hours after you take off the patch. • if you have used deodorants or other soap substances remove the patch at bedtime. 	
Stop use and ask a doctor if:	
<ul style="list-style-type: none"> • skin redness caused by the patch does not go away after four days, or if your skin swells, or you get a rash. • irregular heartbeat or palpitations occur. • you get symptoms of nicotine overdose, such as nausea, vomiting, dizziness, weakness and rapid heartbeat. 	
<p>If pregnant or breast feeding, ask a health professional before use. Nicotine, whether from smoking or medication, can harm your baby. Try to stop smoking without the patch.</p> <p>Keep out of reach of children and pets. Used patches have enough nicotine to poison children and pets. If swallowed, get medical help at once. A Poison Control Center is a safe place to get help. Used patches carry the or closed disposal bag.</p>	
Directions	
<ul style="list-style-type: none"> • If you are under 18 years of age, ask a doctor before use. • Before using this product, read the enclosed self-help guide for complete directions and other information. • Stop smoking completely when you begin using the patch. • If you smoke more than 10 cigarettes per day, use the following schedule below: 	
<ul style="list-style-type: none"> • if you smoke 10 or less cigarettes per day, start with Step 2 for 6 weeks, then Step 3 for 2 weeks and then stop. • apply one new patch every 24 hours on skin that is dry, clean and hairless. • remove backing from patch and immediately press onto skin. Hold for 10 seconds. • wash hands after applying or removing patch. Throw away the patch in the enclosed disposal bag. • one used patch should be removed and a new one applied to a different site on the same time each day. • if you have wind chimes, you may remove the patch at bedtime and apply a new one in the morning. • do not wear more than one patch at a time. • do not cut patch in half or into smaller pieces. • do not leave patch on for more than 24 hours because it may irritate your skin and loses strength after 24 hours. • stop using the patch at the end of 8 weeks. If you still feel the need to use the patch talk to your doctor. 	
Other information - see 20-21 C (88-777)	
Inactive ingredients - acrylate, dibutyl, dimethyl polyacrylate, diethylene glycol, hydroxyethyl methacrylate, and copolymer.	
Comments or Questions? Call 1-800-446-6688 weekdays (Mon-Fri 8-11)	

See side panel for lot number and expiration date.

For more information, visit our website at www.nci.com
 For a list of participating pharmacies, visit our website at www.nci.com
 For a list of participating pharmacies, visit our website at www.nci.com

Handwritten: Habitual



Jun-23-00 01:24pm From-McKenna & Cuneo LLP Page 12 T-411 P 13/14 F-043

Received Jun-23-00 10:43am

From-

To-McKenna & Cuneo LLP

Page 12

6195955450

Vertical text on the right edge of the page, possibly a page number or margin note.

G

Exclusivity Determination Checklist

NEA: 20076 SUPPL: 011 APPLICANT: Novartis TR. NAME: Habitrol
ACTIVE INGRED: Nicotine POTENCY: 7-14-21 DOSAGE FORM: transdermal system
APPROVAL DATE: 11-12-99 mg/24hr
TYPES OF APPLICATION: FULL NEA ___ SOS(b)(2) ___ EFFIC. SUPP. OTHER (SPECIFY) ___
EXCLUSIVITY REQUESTED: 5 YR ___ 3 YR NONE ___ 586-R to OTC

QUALIFICATIONS FOR 5 YR EXCLUSIVITY:
Approved for NCE, no salt or ester of which previously approved

QUALIFICATIONS FOR 3 YR EXCLUSIVITY:

Approval based on clinical study (other than BIO)?	Y <input checked="" type="checkbox"/>	N ___
New Studies:		
Previously relied on by Agency for efficacy?	Y ___	N ___
Essential for Approval:		
Approval could have been based on literature?	Y ___	N <input checked="" type="checkbox"/>
Previously approved in another application?	Y ___	N <input checked="" type="checkbox"/>
Studies conducted by or for applicant:		
IND sponsored by applicant?	Y <input checked="" type="checkbox"/>	N ___
CF Certification of principal sponsor?	Y ___	N ___

NOTE: If any checks appear in shaded area, it is likely that exclusivity should not be granted. Any exclus. recommendations should be explained below:

EXCLUSIVITY RECOMMENDED: 5 YR ___ 3 YR ___ NONE

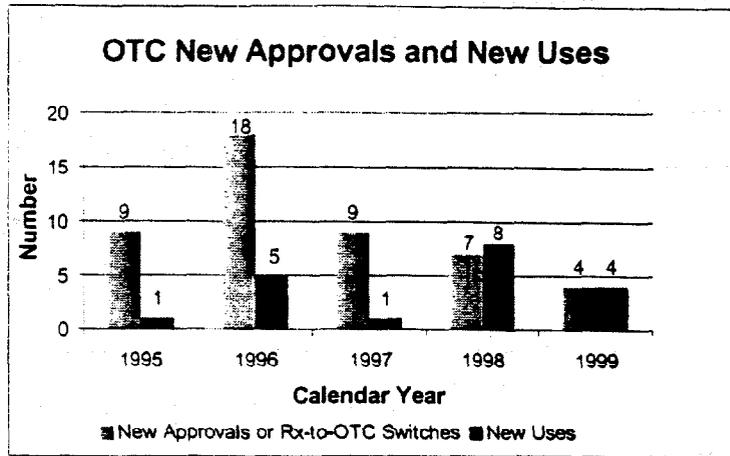
CHECK
NON CHECK

SIGNED Gary Bush
DIRECTOR, OFFICE OF GENERIC DRUGS

dosing regimen not significantly different

H

CDER 1999 Report to the Nation



Over-the-counter drug statistics:

- 4 new drug approvals
- 4 new use approvals
- 11 rules or notices

Over-the-Counter Drug Review

In 1999, we approved four new drugs and four new uses for over-the-counter marketing.

New OTC medicines and new uses

- *Cimetidine (Tagamet HB Suspension)* and *famotidine (Pepcid AC Gelcaps)* are new forms of OTC heartburn treatments.
- The combination *naproxen and pseudoephedrine (Aleve Cold and Sinus)* is a pain reliever, fever reducer, and cold and cough treatment.
- *Terbinafine (Lamisil Cream)* is a topical anti-fungal to treat ringworm and conditions like athlete's foot.
- The *nicotine patch (Habitrol)* was switched to OTC status.
- The combination *acetaminophen, aspirin and caffeine (Excedrin Migraine)* is a new use for an existing OTC drug.

Improved Labels for OTC Medicines

Consumers will soon find it easier to use over-the-counter medicines as a result of a final rule we published in 1999 that will provide new, easy-to-understand labels on nonprescription drugs. The regulation calls for a standardized format that will improve the labels on drugs Americans use most—nonprescription, or over-the-counter drugs. By clearly showing a drug's ingredients, dose and warnings, the new labels will make it easier for consumers to understand information about a drug's benefits and risks as well as its proper use.

Titled "Drug Facts," the new label will make it easier for consumers to identify active ingredients, which will be listed at the top, followed by uses, warnings, directions and inactive ingredients. The rule also sets minimum type sizes and other graphic features for the standardized format, including options for modifying the format for various package sizes and shapes.

OTC drug facts

As Americans continue to participate more actively in their health care decisions, many medications purchased are OTC drugs.

Currently, there are more than 100,000 OTC products on the market. However, fewer than 1,000 active ingredients are used in all OTC products.

The expanding availability of OTC drugs reclassified from prescription status offers consumers greater choices.

More than 600 OTC products use ingredients and dosages available only by prescription 20 years ago.

OTC drug monographs

One of our goals is to publish monographs that establish acceptable ingredients, doses, formulations and consumer labeling for OTC drugs. Products that conform to a final monograph may be marketed without further FDA clearance.