M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: March 9, 2001

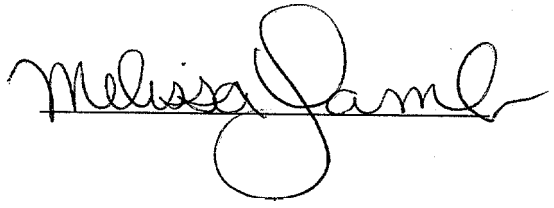
To: Dockets Management Branch (HFA-305)

From: Melissa Lamb
Office of Generic Drugs

Subject: Presentation for the Division of Metabolic and Endocrine Drug Products Journal Club

This memorandum forwards overheads of a presentation to the Dockets Management Branch for inclusion in Docket 90S-0308. The following is information on the presentation for the Docket records:

Title of Presentation:	Waxman-Hatch Marketing Exclusivity and Events Leading up to this Landmark Legislation
Presented for:	Talk on Exclusivity
Date Presented:	March 8, 2001
Presented by:	Donald B. Hare Special Assistant to the Director Office of Generic Drugs Center for Drug Evaluation and Research
Number of Pages:	46



Attachment

90S-0308

M710

Presentation for the Division of Metabolic and Endocrine Drug Products Journal Club

Waxman-Hatch Marketing Exclusivity and Events Leading up to this Landmark Legislation

Donald B. Hare
Special Assistant to the Director
Office of Generic Drugs
Center for Drug Evaluation and Research
March 8, 2001

Grandfathered Drugs/Pre-38 Drugs

Drug Efficacy Study Implementation (DESI) Project

- *NDAs*
- *ANDAs for pre-62 drug products*

OTC Drugs

- *Monograph (Old Drugs)*
- *New Drugs*

NDA/505 (b) Application

May contain literature

Paper NDA (Literature Supported) Application

NDA 505 (b)(1) Application

May contain literature

NDA 505 (b) (2) Application

- *For a change in a listed drug*
- *For a NCE*
- *May contain literature*

Exclusivity Provisions

With the passage of the Drug Price Competition and Patent Term Restoration Act of 1984, market exclusivity was granted to certain new drug applications for innovations. The concept of exclusivity protection and its impact on approval of generic drugs will be discussed.

Patent Provisions

The law now prohibits the approval of generic drugs before the expiration of a patent on the innovator's drug product. Patent protection, challenges and licensing agreements will be reviewed.

Orange Book

The utility of this publication for government agencies, prescribers and dispensers of drug products, the pharmaceutical industry, and managed care providers will be reviewed.

GRANDFATHERED DRUGS/ PRE-38 DRUGS

The FD&C Act of 1938 required that all manufacturers of prescription drug products must thereafter demonstrate the safety of those drug products prior to marketing. This requirement was met through submission of new drug applications (NDAs) containing data to document their safety. Those prescription drug products marketed before 1938 were exempted ("grandfathered") by the Act from obtaining an approval to market. It is believed that few if any pre-38 drug products currently marketed still meet the criteria for "grandfathered" status. The criteria are that there must have been no change in formulation or labeling since 1938. However, the act of reformulation or relabeling a previously grandfathered drug product does not by itself cause such a drug product to be subject to a NDA requirement. The designation of a previously grandfathered drug as a "new drug" is generally accomplished through a Federal Register Notice. A number of medically important grandfathered drugs have been designated as "new drugs" e.g. phenytoin and theophylline through this process.

GRANDFATHERED DRUGS/DRF 28 DRUGS Continued

All Rx drug products approved after 1938 are considered "new drugs".

A "new drug" is defined as drugs which are NOT:

(1) generally recognized as safe
(2) generally recognized as effective
(3) used to a material extent
(4) used for a material time
(See FD&C Act Section 201 (p))

FDA's position is that all Rx drugs are new drugs. Those Rx drug products that are now being marketed without an approved application are being marketed at the firms own risk and regulatory action is presently being deferred.

FDA appealed all the way to the Supreme Court to support this position.

DRUG EFFICACY STUDY IMPLEMENTATION (DESI) PROJECT

- *NDAs*
- *ANDAs FOR PRE-1962 DRUG PRODUCT*

DRUG EFFICACY STUDY [redacted]

A. NDAs

According to the Drug Amendments of 1962 to the FD&C Act, NDAs submitted thereafter had to contain both safety and efficacy data, among other things, to gain approval. In addition, the Drug Amendments required that products approved during the period of 1938-1962, which had been approved on the basis of safety only, had to have each of their indications reviewed for "substantial evidence" of effectiveness. This requirement led to a contract with the National Academy of Science/National Research Council (NAS/NRC) to review the available effectiveness data. The recommendations of NAS/NRC were reviewed by FDA scientists, and Agency conclusions were published in a DESI Federal Register Notice. Firms had to supplement their applications to meet the marketing conditions in the Federal Register Notice before the applications were granted full approval. Drug products in a Federal Register Notice that were declared to lack substantial evidence of effectiveness were removed from the market.

DRUG EFFICACY STUDY IMPLEMENTATION (DESI) PROJECT

There are some DESI drug products that have not been shown to be effective that are in the Notice of Opportunity for Hearing (NOOH) stage, e.g. Donnatal tablets and Librax capsules. These type of DESI drugs are permitted to be marketed while the courts decide their fate.

B. Abbreviated New Drug Applications for Pre-62 Drug Products

An Agency policy was needed for approval of generic drug products without requiring unnecessary repetition of animal or human research that had already been performed to document safety and efficacy of NDA drug products, yet allowing for critical evaluation of the applications. The policy decided upon by the Agency was the Abbreviated New Drug Application (ANDA)procedure. ANDAs were accepted for NDA drug products published inDESI Federal Register Notices and found to be effective by the Agency.The Federal Register Notice would state that the Agency had made a finding that an ANDA was acceptable.

DRUG EFFICACY STUDY [redacted]

The key aspect of that policy was that it would not be necessary for a drug firm to re-prove the safety and efficacy of the active ingredient and dosage form through clinical trials. The ANDA applicant would be relying on the Agency's finding that the listed drug had been shown to be safe and effective. However, to be accepted for ANDA review and approval, the application needed to contain adequate bioequivalence data; complete chemistry, manufacturing, and controls of the drug product through each step of the manufacturing process, starting from the synthesis of the raw materials used to the finished dosage form; assurance that manufacturers comply with current manufacturing practice regulations; assurance that testing and stability date are valid; that the drug substance and finished dosage form meet compendial standards; and that the product is adequately labeled. Prior to the passage of the 1984 Waxman-Hatch Amendment ANDAs were received under the statutory authority of 505 (b).

OTC DRUGS

- monograph (old Drugs)
- New Drugs

OTC drug may be marketed in two different ways:

A. <u>OTC Monographs</u> - *A firm may market an OTC monograph drug with out an approval so long as it meets the provisions of the monograph, e. g. diphenhydramine HCl capsules and acetaminophen tablets. These drug products are considered "Old Drugs".*

B. <u>OTC drugs needing prior approval before marketing (new drugs)</u>

If an OTC drug product is not covered by a monograph it needs an approved application before a firm can market the drug product I.e. ibuprofen tablets 200 mg and cimetidine tablets 100 mg.

The initial agency policy regarding an OTC drug product with Rx indications was that you could not have drug products with both Rx and OTC labeling at the same time. The Rx indications would be handled through professional labeling. The agency has changed that policy and permits a drug product with both Rx and OTC indications to be marketed as a Rx drug product and an OTC drug product e.g. clotrimazole topical cream is marketed as Rx and OTC drug product because it has both Rx and OTC indications; however, clotrimazole vaginal cream, because of the Durham-Humprey amendment can only be OTC because it has only on OTC indication.

505(b) APPLICATION

may contain Literature

A) MAY CONTAIN LITERATURE

- A 505(b) APPLICATION CONTAINS:
  - ***PRECLINICAL***
  - ***CLINICAL***
  - ***CHEMISTRY (CMC)***
  - ***BIOAVAILABILITY DATA***
  - ***LABELING***
  - ***CGMP PROCESS EVALUATION PRIOR TO MARKETING***
- SEE SECTION 505 OF THE FD&C AND 21 CFR SECTION 314.50

PAPER NDA APPLICATION

Literature Supported

This was the procedure that a firm could use to gain approval of a second entry drug first approved after 1962.

The policy was defined as follows:

A drug product marketed for the first time after 1962 under an approved NDA could be marketed by a second firm only after the second firm had received the approval of a full NDA for that product. The agency's policy at that time did not permit ANDAs for this purpose. It was felt that we had the statutory authority for post-1962 ANDAs but regulations had not been written implementing this implied authority as was the case of ANDAs for pre-1962 NDAs.

The law does not allow data in an NDA to be utilized to support another NDA without express permission of the original NDA holder. Thus, in the case of duplicate NDAs for already approved post-1962 drug products, the Agency would accept published literature as the main supporting documentation for safety and effectiveness data. The Agency would not interpret the "full reports of investigations" phrase in the law as requiring either case reports or an exhaustive review of

all published data. However, the Agency reserved the right to request case reports if needed to evaluate the studies reported in the literature. Selected preclinical and perhaps additional clinical studies might be required of the new sponsor prior to NDA approval. In some instances the holder of the Paper NDA could not support the safety and effectiveness of all of the indications in the original NDA. Therefore the labeling of the Paper NDA would be different from the original NDA regarding the number of approved indications.

This policy was initially announced in a memorandum, dated July 31, 1978, entitiled "NDAs for Duplicate Drug Products of Post-1962 Drugs". It was memorialized in a Federal Register Notice dated May 19, 1981.

The Agency Was sued over this issue by Burroughs Wellcome Company
and prevailed.

PA

The regulations implementing the Waxman-Hatch Amendments revoked the Paper NDA policy since it was no longer needed. Congress provided the Agency with clear statutory authority to extend its ANDA policy to cover all NDAs that had been approved for safety and effectiveness regardless of their approval date.

505(B)(1) APPLICATION

505(b)(1) Applications

A 505(b)(1) Application contains the following:

- *Preclinical*
- *Clinical*
- *Pediatric Use*
- *CMC Data*
- *Bioavailability Data*
- *Labeling*
- *Patent Information*
- *(May Request Exclusivity)*
- *CGMP*

505(b)(2) APPLICATION

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A short definition of a 505(b)(2) application is an application that is submitted under 505(b)(1) and the studies necessary for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference.

There are two types of 505(b)(2) applications: (1) rarely used for a NCE and (2) mainly used for a change in a listed drug.

A 505(b)(2) Application for a change in a listed drug contains and relies upon:

- *The Agency's Finding of Safety and Efficacy of the Listed Drug*
- *Preclinical - references the agency's finding of S&E and whatever safety data needed to support the change*
- *Clinical - whatever clinical data is needed to support the change*
- *Pediatric Use*
- *CMC Data*

Comparative Bioavailability Data - Just as an ANDA has to do a bioequivalence study to use the agency's finding of safety and efficacy of the listed drug a 505(b)(2) applicant has to do a comparative bioavailability study using the listed drug as one of the arms of the study. If necessary to support the change additional PK data may be requested.

- *Labeling*
- *Submit Patent Information*
- *(May Request Exclusivity)*
- *Patent Certification*
- *Exclusivity Statement*
- *CGMP*

As mentioned previously the Waxman-Hatch Regulations revoked the "Paper NDA" policy. Even though the two terms, "Paper NDA" and a 505(b)(2) application, are sometimes used interchangeably, it is incorrect to do so.

WAXMAN-HATCH AMENDMENTS

WAXMAN-HATCH AMENDMENTS ENACTED SEPTEMBER 24, 1984

Center Director Letters

Title I Proposed Rule — **July 10, 1989**

- **Review and Approval Requirements** — **April 28, 1992**
- **Patent and Exclusivity Provisions** — **October 3, 1994**

DRUG PRICE COMPETITION & PATENT TERM RESTORATION (DCP&PTR) ACT OF 1984

- *Statutory authority for FDA approval of pre-and post-1962 generic drugs*
- *Make available high-quality, low-cost generics-reducing health care costs*
- *Eliminate costly and unnecessary duplicative safety and efficacy studies*
- *Assure continued development of new drugs through patent extension and exclusivity granted to certain NDAs*

COMPROMISE

Title I

- *More Drug Products Eligible for ANDAs*
- *Reduce Costs of Health Care*
- *180 Day Exclusivity for Generic Drugs*
- *NDA Exclusivity and Patent Protection*
- *"Old" Antibiotics Not Covered*

Title 2

- *Promote Development of New Drugs*
- *Up to Five Years of Patent Extension*

EXCLUSIVITY PROVISIONS

- *Orphan Drug Exclusivity (ODE) - 7 years*
- *New Chemical Entity (NCE) - 5 years*
- *"Other" exclusivity - 3 years for a "significant change" if criteria are met*
- *Pediatric exclusivity (PED) - 6 months added to existing patents or exclusivity*

Exclusivity

Orphan - upon approval of designated orphan drug - Office of Orphan Products issues letter when exclusivity granted - separate from other types of exclusivity

PE

A period of 6 months exclusivity is added to any existing exclusivity or patents on all applications held by the sponsor for that active moiety

Pediatric exclusivity does not stand alone

WAXMAN-HATCH
MARKET EXCLUSIVITY

Granted to NDA's Only

Delays Final Approval of an ANDA

Delays Submission of an ANDA

Independent of: Patent Protection or Ophan Drug Exclusivity

Can Run Concurrently

NEW CHEMICAL ENTITY (NCE) PROTECTION

10 Year (NCE Approved Between 1/1/82 and 9/24/84)

5 Year (NCE Approved After 9/24/84)
Cannot File an ANDA for 5 years

TECTION

2 Year - Change Approved Between 1/1/82 and 9/24/84

3 Year - Significant Change Approved After 9/24/84

- ***Original NDA or Supplement***
- ***New Clinical Studies (other than bioavailability studies)***
- ***Essential for Approval***
- ***Conduct by Applicant***
- ***Examples of Changes (active ingredient, strength, dosage form, route of administration, indication, dosing regimen, Rx to OTC switch)***

PATENT PROVISIONS

When and Where to submit:

- ***With Original Application***
- ***Supplements - Patented changes including new formulation, new indication, new condition of use, new strength***
- ***After approval - 30 days from date of issue of patent for timely filing***

-ING

Applies to NDA's Only

Delays Final Approval Date of ANDA

Patents Covered

Drug Product: ***Formulation, Composition***

Drug Substance: ***Active Ingredient***

Method of Use: ***Indication***

Filing Requirement: NDAs and Some Supplements

Published in Orange Book

PA[redacted]FICATION

Applies to ANDA's
Certifications

- ***I*** ***Patent Not Submitted to FDA***
  Immediately Effective Approval Date
- ***II*** ***Patent Expired***
  Immediately Effective Approval Date
- ***III*** ***Patent Expiration Date***
  Tentative Approval
- ***IV*** ***Patent Challenge***

No Relevant Patent

Method of Use Patent Does Not Claim Patented Use

Patents

- *Listed in the Orange Book as per the Applicant holder's submission*
- *Granted by U.S. Patent and Trademark Office at anytime in the "life" of a drug*
- *Expire 20 years from date of patent filing*
- *Approximately 240 patents listed in the Orange Book will expire in the next 5 years*

Patents

- *Third parties may challenge listing of patent*
- *Application holder ultimately determines changes necessary to Orange Book listing*

Patents

- *Agency lack of expertise in patent law-cannot conduct meaningful oversight*
- *Disputes resolved in Court-Agency does not act as Intermediary/Referee*

- *Exclusivity and Patents May or May not Run Concurrently*
- *NDAs May Have "Shared" Waxman Hatch Exclusivity*
- *Applicant Not Required to Request Exclusivity*
- *Agency Obligated to Make Exclusivity Determination on All Relevant Applications*

ORANGE BOOK

APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS

"Orange Book"

Drug Products listed in Orange Book

- *Approved for Safety and Efficacy*
- *NDAs - includes antibiotics*
- *ANDAs*
- *AADAs*

Drug Products not listed in the Orange Book

- *Pre-1938*
- *DESI drug products for which efficacy has not been demonstrated*

APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS

Orange Book is published annually with 12 cumulative monthly subjects. The current edition is the 20th

- *Some examples of the Orange Book sections:*
  - *Prescription Drug Product List*
  - *OTC Drug Product List*
  - *Discontinued Drug Product List*
  - *Orphan Drug Product Designations*
  - *Patent and Exclusivity Lists*