

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022432Orig1s000

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: September 27, 2010

To: Susan Daugherty
Senior Regulatory Health Project Manager
DNP

CC: Mary Dempsey
Project Management Officer
OSE, DRISK

Sharon Mills
Acting Team Leader
OSE, DRISK

From: Sharon Watson, PharmD
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

Subject: Drug: H.P. Acthar[®] Gel (Repository Corticotropin)
NDA: 022432

DDMAC has reviewed the 9/24/10 DRISK review of the proposed Medication Guide (Med Guide) for H.P. Acthar Gel in comparison with the proposed FDA-approved product labeling (PI). DDMAC's comments are provided directly on the clean version of this proposed Med Guide document, attached below.

Thank you for the opportunity to comment on this proposed Med Guide.

If you have any questions or concerns regarding these comments, please contact me.

7 Page(s) of Draft Labeling has been
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/s/

SHARON M WATSON
09/27/2010

Internal Consult

Pre-decisional Agency Information

To: Russell Katz, MD, Director, Division of Neurology Products (DNP)
Norman Hershkowitz, MD, Team Leader, DNP
Susan B Daugherty, Senior Regulatory Project Manager, DNP

From: Quynh-Van Tran, PharmD, BCPP
Regulatory Reviewer, Division of Drug Marketing, Advertising, and
Communications, (DDMAC)

CC: Andy Haffer, PharmD, Group Leader, DDMAC

Date: September 24, 2010

Re: Comments on draft labeling (Package Insert) for H.P. Acthar Gel
(repository corticotropin) Injection

NDA 22-432

Thank you for the opportunity to review the proposed PI for H.P. Acthar Gel (FDA dated version 9/20/2010). Please see attached PI with our comments incorporated therein.

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/s/

QUYNH-VAN TRAN
09/27/2010

CLINICAL CONSULTATION

DATE CONSULT RECEIVED: Jan. 19, 2010

DATE CONSULT COMPLETED: May 26, 2010

FROM: William Lubas, MD-PhD, Medical Officer
Division of Metabolism and Endocrinology Products, HFD-510

THROUGH: Dragos Roman, MD, Team Leader, DMEP
Mary Parks, MD, Division Director, DMEP

TO: Susan Daugherty, RPM
Division of Neurology Products

SUBJECT: PLR review of H.P. Acthar Gel

MATERIAL EVALUATED IN THIS REVIEW

- The consult request from Division of Neurology Products
- Latest PLR version of submitted to the EDR on April 28, 2010
\\FDSWA150\NONECTD\N22432\N_000\2010-04-28
- [H.P. Acthar Gel and Cosyntropin Review: Clinical and Financial Implications.](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2697107/pdf/ptj34_5p250.pdf)
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2697107/pdf/ptj34_5p250.pdf
- PLR version of Flo-Pred (prednisolone acetate) steroid class label
<http://dartrts/dartrts/ViewDocument?documentId=090140af801d4109>

INTRODUCTION

H. P. Acthar Gel (Repository Corticotropin Injection) contains the full length 39-amino acid human native ACTH molecule in a 16% gelatin gel to provide for prolonged release after intramuscular or subcutaneous injection. Endogenous ACTH stimulates the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and a number of weakly androgenic substances. It is presumed that the mechanism of action of H. P. Acthar Gel is most likely mediated by the relative increase in production of these individual steroid hormones, however, the exact mechanism of action for specific indications, such as treatment of infantile spasms, is not known.

Repository Corticotropin Injection was originally approved in 1952 for a variety of disorders and diseases that at the time were thought to benefit from steroid mediated immunosuppression including:

COLLAGEN DISEASES - Acute Lupus Erythematosus; Psoriatic Arthritis;
Rheumatoid Arthritis; Rheumatic Fever; Rheumatoid Spondylitis; Still's Disease.

HYPERSENSITIVITIES – Acquired Hemolytic Jaundice, Angioneurotic Edema, Contact Dermatitis, Drug Sensitivities, Severe Bronchial Asthma, Severe Hay Fever, Urticaria.

ACUTE INFLAMMATORY DISEASES OF THE EYE - Acute Secondary Glaucoma; Choroiditis; Conjunctivitis; Iritis; Keratitis; Optic Neuritis; Sympathetic Ophthalmia; Uveitis.

ACUTE INFLAMMATORY DISEASES OF THE SKIN – Acute Psoriasis unresponsive to usual treatment, Exfoliative Dermatitis, Severe Pemphigus.

NEPHROTIC SYNDROME

METABOLIC DISEASES – Acute Gouty Arthritis, Congenital Idiopathic Hypoglycemia.

ULCERATIVE COLITIS

ALCOHOLISM AND DELIRIUM TREMENS

BURNS

BURSITIS; TENOSYNOVITIS

PANHYPOPITUITARISM

OTHER USES – ACTHAR (Corticotropin) preparation have also been used in numerous other disease states, such as: Diagnosing adrenal cortical insufficiency and Addison's disease, Acute Leukemia and Chronic Lymphatic Leukemia; Acute Overwhelming Infections; Agranulocytosis; Beryllium Poisoning; Guillain-Barre Syndrome; Hodgkin's Disease; Loeffler's Syndrome; Stevens-Johnson Syndrome; Radiation Sickness, and Vasomotor Rhinitis.

The initial approval of H.P. ACTH gel occurred prior to the Kefauver-Harris amendment to the Federal Food, Drug and Cosmetic Act of 1962, which introduced the requirement of "substantial evidence" of two adequate and well controlled trials. At the time of the original approval drug manufacturers only had to show the drug was safe for use in humans. The original data included case reports from a few physicians describing patients with conditions originally treated with Acthar powder that were transferred to treatment with Acthar Gel and gave dosing guidance for treatment of these individual conditions. A few patients had improvements in hematology data and improvement in symptoms (decreased diarrhea, improved appetite, sense of well being, etc.) reported to support the efficacy of treatment. Additional indications for sarcoidosis, anogenital pruritis, nonsuppurative thyroiditis, and nontropical sprue were added in 1954 using additional information from case reports in the literature. These data would be grossly

inadequate to support approval of a new drug or new indications by the Agency under current standards requiring evidence from adequate and well-controlled clinical trials.

A Drug Efficacy Study Implementation (DESI) review of corticotrophin injection was initiated in 1971 and finalized in 1977. Changes to the package insert as part of the initiation of the DESI review in 1971 included the following:

H.P. ACTHAR® GEL (Repository Corticotropin Injection) is indicated for diagnostic testing of adrenocortical function.

H.P. ACTHAR GEL® (Repository Corticotropin Injection) has limited therapeutic value in those conditions responsive to corticosteroid therapy; however, corticosteroid therapy is considered to be the treatment of choice. H.P. ACTHAR® GEL (Repository Corticotropin Injection) may be employed in the following disorders:

RHEUMATIC DISORDERS: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: Psoriatic arthritis, Rheumatoid arthritis; Ankylosing spondylitis; Acute and subacute bursitis; Acute nonspecific tenosynovitis; Acute gouty arthritis.

COLLAGEN DISEASES: During an exacerbation or as maintenance in selected cases of Systemic lupus erythematosus; Systemic Dermatomyositis (polymyositis); Acute Rheumatic carditis.

DERMATOLOGIC DISEASES: Pemphigus; Bullous dermatitis herpetiformis; Severe erythema multiforme (Stevens- Johnson syndrome); Exfoliative dermatitis; Severe psoriasis.

ALLERGIC STATES: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment— Seasonal or perennial allergic rhinitis; Bronchial asthma; Contact dermatitis; Atopic dermatitis; Serum sickness.

OPHTHALMIC DISEASES: Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: Allergic conjunctivitis; Keratitis; Herpes zoster ophthalmicus Iritis; Diffuse posterior uveitis and choroiditis; Optic neuritis; Sympathetic ophthalmia.

RESPIRATORY DISEASES: Symptomatic sarcoidosis; Loeffler's syndrome not manageable by other means; Berylliosis.

HEMATOLOGIC DISORDERS: Acquired (autoimmune) hemolytic anemia.

NEOPLASTIC DISEASES: For palliative management of: Leukemias and lymphomas in adults; Acute leukemia of childhood.

EDEMATOUS STATE: To induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.

MISCELLANEOUS: Tuberculous meningitis with subarachnoid block or impending block when concurrently accompanied by appropriate antituberculous chemotherapy. Trichinosis of neurologic or myocardial involvement.

ACTHAR® (Corticotropin Injection) and H.P ACTHAR® GEL (Repository Corticotropin Injection) may also be useful in the following conditions:

METABOLIC DISORDER: Congenital idiopathic hypoglycemia.

ALLERGIC STATES: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment: Angioedema; Urticaria.

RESPIRATORY DISEASES: Pulmonary emphysema where bronchospasm or bronchial edema plays a significant role.

GASTROINTESTINAL DISEASES: To tide the patient over a critical period of the disease in: Ulcerative colitis; Crohn's disease; Intractable sprue.

HEMATOLOGIC DISORDERS: Infectious mononucleosis

The following additional indications were added in 1977 as part of S-016:

ENDOCRINE DISORDERS: Nonsupportive thyroiditis; Hypercalcemia associated with cancer.

RHEUMATIC DISORDERS: Post-traumatic arthritis; Synovitis of osteoarthritis; Epicondylitis.

DERMATOLOGIC DISEASES: Severe seborrheic dermatitis; Mycosis fungoides.

OPHTHALMIC DISEASES section: Iridocyclitis; Chorioretinitis; Anterior segment inflammation; Allergic corneal marginal ulcers.

RESPIRATORY DISEASES section: Fulminating or disseminated pulmonary tuberculosis when used concurrently with antituberculous chemotherapy; Aspiration pneumonitis.

HEMATOLOGIC DISORDERS section: Idiopathic thrombocytopenia purpura in adults (i.v. only; I.M. is contraindicated); Secondary thrombocytopenia in adults; Erythroblastopenia (RBC anemia); Congenital (erythroid) hypoplastic anemia.

GASTROINTESTINAL DISEASES section: Regional enteritis.

MISCELLANEOUS section: Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy. Trichinosis of neurologic or myocardial involvement.

An additional indication for the treatment of acute exacerbations of multiple sclerosis was added in 1979, S-018.

The indication for use in ITP was removed as part of S-024 in 1981.



Supplement SLR-039 in June of 2006 again sought to add the indication for the treatment of infantile spasms. This time the sponsor submitted a literature review and a meta analysis of eight randomized controlled trials. A May 2007 review by Drs. Schragger, Kehoe and Parks in DMEP again concluded that [redacted] (b) (4) [redacted] (b) (4) H.P. Acthar gel and a Not Approvable letter was issued. It was recommended that the sponsor address these deficiencies with a resubmission to the Division of NeuroPharmacology Products.

A complete response to NDA 08-372, SLR-039 was submitted under NDA 22-432 in March 2009. This includes a reanalysis of the most relevant publication (Baram 1996) and a retrospective chart review to support their currently proposed dosing scheme for infantile spasms.

No specific questions were included as part of this consult request. DMEP was instead asked to review the latest PLR version of the label for clarity and correctness.

REVIEW

Diagnostic Testing of Adrenocortical Function

The current package insert recommends the use of H.P. Acthar Gel for diagnostic testing of adrenocortical function; however, there is no reference to support the proposed indication. The dosing recommendation suggests that doses of as much as 80 units as a

single injection, or more injections of a lesser dose, may be used but that dosage and frequency should be individualized without giving any recommendations on how that should be done. It also gives no information on how to interpret the test results.

A review of the PubMed literature by this medical reviewer failed to identify any current references that refer to the use of the ACTH Acthar Gel for adrenocortical function testing. A 1995 version of de Groot and Jameson did mention the use of an alternative 48hr ACTH Infusion Test, but concluded that “the test requires hospitalization to perform and mainly for that reason has become obsolete in the differential diagnosis of adrenal insufficiency.” In addition, Acthar Gel is contraindicated for IV infusion and the ACTH Infusion Test would have required the use of Acthar Powder which is no longer marketed. Other current references such as: De Groot, William’s, Harrison’s, the Merck Manual and ACP PIER & AHFS DI, instead recommend the currently approved cosyntropin test for adrenocortical function testing. This test has the advantage that in most cases the result can be obtained 30 minutes after the IV injection. Even the diagnosis of secondary adrenal insufficiency which might benefit from a longer testing period is recommended to be performed by standard short-term cosyntropin testing after several days of short term priming of the adrenal. Therefore, it is this medical reviewer’s conclusion that the current evidence to support the dose and testing of adrenocortical function with Acthar Gel is inadequate and that this indication should be removed during the PLR conversion. If the sponsor wishes to maintain this indication, they should submit data to support a validated testing procedure. These data must include information on how to determine the appropriate testing dose and how to interpret the study results to conclude a diagnosis of adrenal insufficiency.

Endocrine Disorders

The current package insert includes two endocrine disorders with indications for treatment with H.P. Acthar Gel: nonsuppurative thyroiditis and hypercalcemia associated with cancer. Neither of these is a common indication for the use of Acthar Gel in current clinical practice. Painful subacute thyroiditis is usually treated with NSAIDs and if that fails prednisone is an alternative. Hypercalcemia associated with cancer is treated with intravenous hydration, diuretics, bisphosphonates, and gallium nitrate. Steroids can be useful in cases of multiple myeloma and lymphoma but as previously discussed there is no benefit to the use of H.P. Acthar therapy over standard steroid treatment. The original approval of H.P. Acthar Gel did not include these specific indications, nonsuppurative thyroiditis and hypercalcemia associated with cancer, and they were added in a later supplement using case reports from that literature as the supportive evidence.

A search in PubMed by this medical reviewer for references supporting the use of ACTH/corticotrophin for these endocrine indications was unsuccessful. For example: A search using the keywords. “ACTH” and “nonsuppurative thyroiditis” retrieved three references: two foreign and one in English (from Nov. 1953) but none had abstracts available on line for review. A search for the keywords “ACTH” and “hypercalcemia” and “cancer” identified 84 references, none of which referred to ACTH as a potential treatment for hypercalcemia associated with cancer. As there is inadequate evidence to support the safe and effective use of H. P. Acthar Gel for these specific endocrine

indications, DMEP would recommend removal of these indications from the package insert during the PLR conversion.

Use in Children over 2 years of Age and Adults for Indications Other than Infantile Spasms and Multiple Sclerosis

The question arises whether there is sufficient evidence to support the other potential indications in the following categories: nervous system, rheumatic, collagen, dermatologic, allergic states, ophthalmic, respiratory, hematologic, neoplastic, edematous, gastrointestinal, and miscellaneous, which are currently part of the H.P. Acthar Gel package insert. A search of Pubmed using the keyword “acthar” identified only 11 references of which only three reports dealt specifically with possible treatment indications: infantile spasms¹, hay fever² and sarcoidosis³. A recent review of the clinical utility of H.P. Acthar Gel, by Gettig et al.⁴, which included an extensive search of the literature, confirmed that there are currently only three potential common uses for this medication despite the extensive list of potential uses included in the package insert. They include adrenocortical function testing, treatment of infantile spasms and treatment of multiple sclerosis. As the PLR conversion of the package insert offers an opportunity to reassess the quality of the evidence used to support the current indications it seems reasonable to recommend removal of these unsupported indications. The sponsor should be encouraged to submit evidence of adequate and well controlled trials to support any of these indications that they wish to retain. Consideration of the evidence in support of these other indications should be directed to the appropriate review division which has expertise in the particular medical condition (e.g., severe seborrheic dermatitis should be reviewed by the Division of Dermatology and Dental Products).

Use in Adults for Multiple Sclerosis

The current package insert recommends daily intramuscular injections of 80 -120 Units for 2-3 weeks for the treatment of acute exacerbations of multiple sclerosis. It is recommended that the Division of NeuroPharmacology review the PLR conversion for this indication.

¹ [Discharge planning for the child with infantile spasms](#). Kongelbeck SR. J Neurosci Nurs. 1990 Aug;22(4):238-44.

² [Comparison of a low and high dose ACTH gel in the treatment of hay fever](#). Parr EJ, Davies BH. Clin Allergy. 1980 Mar;10(2):195-202.

³ [Effect of Acthar-c \(ACTH\) in sarcoidosis](#). MILLER MA, BASS HE. Ann Intern Med. 1952 Oct ; 37(4):776-84

⁴ [H.P. Acthar Gel and Cosyntropin Review: Clinical and Financial Implications](#).

Gettig J, Cummings JP, Matuszewski K. P T. 2009 May;34(5):250-257.

LABELING RECOMMENDATIONS

Highlights Section INDICATIONS AND USAGE

Delete the initial indication for [REDACTED] (b) (4)

Replace the second paragraph:

- [REDACTED] (b) (4)

with the following:

- H.P. Acthar Gel may be used for the treatment of acute exacerbations of multiple sclerosis.

DOSAGE AND ADMINISTRATION

Delete the first two paragraphs describing [REDACTED] (b) (4)

WARNINGS AND PRECAUTIONS

Revise to more closely resemble recent PLR class labeling for steroids.

USE IN SPECIFIC POPULATIONS

Delete the section on nursing mothers.

1 INDICATIONS AND USAGE

Delete the second paragraph describing [REDACTED] (b) (4)

Replace the third paragraph:

[REDACTED] (b) (4)

with the following:

Use in Adults: H.P. Acthar Gel (repository corticotropin injection) is indicated for the treatment of exacerbations of multiple sclerosis.

Delete sections 1.1 to 1.15

2 DOSAGE AND ADMINISTRATION

Section 2.1- delete all but the last paragraph describing use in the treatment of exacerbations of multiple sclerosis, and revise according to Neuropharmacology recommendations.

Section 2.2- recommend revision by Neuropharmacology which is reviewing the infantile spasms indication.

5 WARNINGS AND PRECAUTIONS

Recommend revising this section to more closely resemble steroids class labeling (see recent PLR conversion for Flo-Pred). For example there is currently no mention of GI perforation, negative effects on bone density, negative effects on growth and development in pediatric patients, behavioral or mood disturbances, hypothalamic-pituitary-adrenal axis suppression, risk for fetal harm, Cushing's syndrome and hyperglycemia in the current WARNINGS AND PRECAUTIONS section.

8 USE IN SPECIFIC POPULATIONS

Renumber sections: Nursing Mother to 8.3 and Pediatric Use to 8.4 as per labeling guidance.

14 CLINICAL STUDIES

Recommend that Neuropharmacology revise this section to support the two revised indications: infantile spasms and multiple sclerosis.

15 REFERENCES

Delete this section as per recent labeling guidance.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICA LS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

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/s/

WILLIAM A LUBAS
05/28/2010

DRAGOS G ROMAN
05/28/2010

MARY H PARKS
05/28/2010

505(b)(2) ASSESSMENT

Application Information		
NDA # 022432	NDA Supplement #: S- n/a	Efficacy Supplement Type SE- 1
Proprietary Name: H.P. Acthar Gel Established/Proper Name: (repository corticotropin injection) Dosage Form: injection Strengths:		
Applicant: Questcor Pharmaceuticals		
Date of Receipt: June 23, 2006		
PDUFA Goal Date: June 11, 2010		Action Goal Date (if different):
Proposed Indication(s): Infantile Spasms		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

H.P. Acthar Gel (repository corticotropin injection) is a highly purified sterile preparation of the adrenocorticotrophic hormone, however, this product is regulated as a drug per 21 CFR 3.5.

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

N/A

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4©.

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.
If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

- YES NO Patent owner(s) consent(s) to an immediate effective date of approval