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SUBMITTED ELECTRONICALLY

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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

CITIZEN PETITION

The undersigned, on behalf of Bracco Diagnostics Inc., submits this Citizen Petition electronically with respect to section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA") and in accordance with 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs take the actions described below.

I. Action Requested

We respectfully request that the Food and Drug Administration ("FDA") make a determination that the two-ingredient formulation of KINEVAC for injection was discontinued for safety and efficacy reasons. The two-ingredient formulation proved to be unstable, increasing the risk that when used as an intended diagnostic it could result in false positives leading to unnecessary surgery. The discontinued formulation, as originally approved by the agency, contained 5 µg sincalide with 45 mg sodium chloride to provide tonicity using sodium hydroxide or hydrochloric acid to adjust pH to 5.5 to 6.5.

The petitioner specifically requests that FDA make a determination (i) that the two-ingredient formulation was discontinued for safety and efficacy reasons, and (ii) that any proposed generic product referring to the discontinued two-ingredient formulation would result in a product that is less safe and effective than the KINEVAC formulation currently marketed by Bracco Diagnostics Inc. ("Bracco") under NDA 17-697/S-013 approved on November 27, 2002. The petitioner further requests that FDA determine that the discontinued formulation is not a suitable reference drug for an Abbreviated New Drug Application ("ANDA"), and that FDA shall not accept for review or approve any ANDA that refers to the discontinued two-ingredient formulation of KINEVAC for injection.

II. Statement of Grounds

A. Regulatory Background

The ANDA process under which generic drugs are approved and marketed in the United States is codified in Section 505(j) of the FDCA. Section 505(j)(4) provides:

> [T]he Secretary shall approve an application for a drug unless the Secretary finds—
>
> (A) the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity;…
>
> (H) information submitted in the application or any other information available to the Secretary shows that (i) inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included…[1]

Under this statutory framework, an ANDA applicant may obtain FDA approval of a drug that is the "same" as a previously approved drug without conducting the full battery of clinical and non-clinical studies that are required for a New Drug Application ("NDA").[2] An ANDA applicant is allowed to rely upon a prior FDA finding of safety and efficacy for the approved drug that is referenced by the ANDA applicant, provided that the proposed generic drug is the same as the approved drug with regard to active ingredients, dosage form, route of administration, strength, and labeling.[3] The proposed generic drug also must be demonstrated to be bioequivalent to the referenced drug.[4]

Additionally, ANDA applicants must reference a suitable "listed drug," which FDA regulations define as "a new drug product…which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness…"[5] The particular "listed drug identified by FDA as the drug product upon which an [ANDA] applicant relies" is further defined as the "reference listed drug" ("RLD").[6] FDA will not accept for review or approve ANDAs that refer to a drug product that the agency determines has been withdrawn from sale for

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[1] FDCA § 505(j)(4)(A), (H).

[2] *See generally* FDCA § 505(j).

[3] FDCA § 505(j)(2)(A)(i), (ii), (iii), and (v).

[4] FDCA § 505(j)(2)(A)(iv); 21 C.F.R. § 314.127(a)(6)(i).

[5] 21 C.F.R. § 314.3(b).

[6] *Id.*

reasons of safety and effectiveness.[7] FDA regulations describe safety and effectiveness data to "include all studies and tests of a drug on animals and humans and all studies and tests of the drug for identity, stability, purity, potency, and bioavailability."[8] "A determination whether a listed drug that has been voluntarily withdrawn from sale was withdrawn for safety or effectiveness reasons may be made by the agency at any time after the drug has been voluntarily withdrawn from sale, but must be made [p]rior to approving an [ANDA] that refers to the listed drug…"[9]

B. Factual Background

KINEVAC is a cholecystopancreatic-gastrointestinal hormone peptide for parental administration. The active pharmaceutical ingredient ("API"), sincalide, is a synthetically-prepared C-terminal octapeptide of cholecystokinin ("CCK"), with the following amino acid sequence: Asp-Tyr(SO_3H)-Met-Gly-Trp-Met-Asp-Phe-NH_2. Sincalide is the biologically active moiety of the natural CCK molecule, and binds to receptors that stimulate contraction of the smooth muscle in the walls of the gallbladder and small bowel. The main clinical use of KINEVAC is to induce emptying of the gallbladder as part of a diagnostic test called functional cholescintigraphy. The purpose of this test is to determine whether the gallbladder should be surgically removed due to functional gallbladder disorder ("FGBD") in patients who have an ultrasonographically normal appearing gallbladder.

The discontinued formulation of KINEVAC was approved by FDA in 1976 under an NDA first filed by E.R. Squibb & Sons, Inc. and later held by Bristol-Myers Squibb. From the time of its introduction, FDA raised concerns about manufacturing and analytical issues regarding the now discontinued two-ingredient formulation. FDA expressed particular concerns about the stability and potency of the two-ingredient formulation. In a letter to E.R. Squibb & Sons, Inc. FDA stated: "We request that you investigate the reasons for this stability problem and…propose a solution."[10] Indeed, for several years, product accommodations which were not disclosed in the label were made at the request of FDA to temporarily address the stability problem. FDA permitted the NDA holders to manufacture the now discontinued KINEVAC product with certain overages that were not included in the label pending permanent resolution of the stability problem with the two-ingredient formulation.

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[7] FDA Draft Guidance for Industry, "Referencing Approved Drug Products in ANDA Submissions (January 2017), at 4-5 (explaining that a discontinued drug "may be eligible to be an RLD, unless FDA makes a determination that the listed drug was withdrawn from sale for reasons of safety or effectiveness. If FDA makes such a determination, the listed drug will be removed from the Orange Book and is no longer eligible to be an RLD.").

[8] 21 C.F.R. § 314.430(a).

[9] 21 C.F.R. § 314.161(a)(1).

[10] *See* Letter from Stewart J. Ehrreich, Deputy Director, Division of Cardio-Renal Drug Products, Office of Drug Research and Review, Center for Drugs and Biologics, Food and Drug Administration, to Charles L. Kroll, Director, Regulatory Operations, E.R. Squibb & Sons, Inc., September 18, 1984.

In 1994, the KINEVAC NDA was transferred to Bracco. Bracco subsequently submitted a supplemental NDA for KINEVAC that incorporated product changes to resolve these outstanding FDA issues. Such product changes included a new formulation of the drug product with the addition of excipients to maintain the stability of the peptide in both bulk solution and final lyophilized product. In addition to addressing stability issues, the reformulated product eliminated the requisite overages that had been incorporated into the discontinued two-ingredient formulation as a stopgap measure to address FDA's concerns about the instability of the two-ingredient formulation.

The shelf life of both the discontinued KINEVAC formulation and the currently marketed KINEVAC formulation is listed as 18 months. Within this period of time, the discontinued unstable formulation degraded significantly. By contrast, the currently marketed formulation of KINEVAC has been shown to be relatively stable.

The assay in the NDA for the discontinued formulation is the USP potency method for sincalide for injection. It is a bioassay which measures the gallbladder contractile responses in guinea pigs following intravenous administration of product. Using this assay, three batches of the discontinued formulation have been tested and shown to degrade at an average rate of more than 20% over the 18-month shelf life. The sincalide assay stability (25°C) profiles for three commercial lots of the discontinued formulation demonstrated that the period of time in which the amount of sincalide fell from 5 µg to the NDA standard limit of 4.25 µg ranged from 9.7 months to 16.7 months. Specifically, samples with initial amounts of 5.85 µg, 5.2 µg, and 4.9 µg sincalide degraded at rates of 27.8%, 17.3%, and 16.1 %, respectively. Based on these degradation rates, samples containing 5 µg sincalide fell below 4.25 µg in 9.7, 15.6, and 16.7 months, respectively, all of which are shorter than the FDA-approved shelf life of 18 months.

The assay for the currently marketed KINEVAC formulation is an HPLC method suitable as a stability-indicating method to monitor the degradation profile of sincalide. Using this assay, batches of the currently marketed formulation have been tested and shown to be consistently and significantly more stable than the discontinued formulation. The sincalide assay stability (25°C) profiles for three commercial lots of the currently marketed formulation remained within the 4.5 µg/vial limits through 24 months. This is a substantial improvement over the stability profiles shown for the discontinued formulation. Moreover, the currently marketed formulation – unlike the discontinued formulation - does not contain an overage that would render the product labeling inaccurate.

C. Argument

1. Bracco discontinued the two-ingredient KINEVAC formulation for safety and effectiveness reasons after it developed a more stable formulation

Bracco discontinued the two-ingredient KINEVAC formulation after it developed the more stable currently marketed formulation, because the instability of the old formulation limited

its clinical effectiveness as a diagnostic tool for patients contemplating gallbladder surgery. Cholecystokinin-stimulated cholescintigraphy ("CCK-CS") with measurement of gallbladder ejection fraction ("GBEF") is the standard in clinical practice for diagnosing FGBD.[11] During this diagnostic procedure, a technetium (Tc-99m)-labeled radiopharmaceutical is taken up by the liver and excreted into the biliary system where it accumulates in the gallbladder. A GBEF is then calculated after stimulating gallbladder emptying with CCK. An abnormally low GBEF is indicative of FGBD, therefore CCK-CS aids in the decision whether to proceed with cholecystectomy in patients presenting with suspected biliary pain and anatomically normal appearing gallbladder.[12]

Clinicians have recognized that the safety and efficacy of KINEVAC significantly depend on its stability and potency. Degradation of an unstable sincalide formulation "may result in less than the expected amount of sincalide available for injection, which could result in falsely low gallbladder emptying that might be misinterpreted as chronic colecystitis."[13] By the same token, super-potent sincalide can increase the frequency and severity of side effects, while sub-potent sincalide can result in falsely low GBEF measures and misdiagnoses of gallbladder dysfunction.[14]

Because of the stability problem with the two-ingredient formulation, vials of KINEVAC containing the two-ingredient formulation contained drug product of variable potency depending on the length of time that a particular vial had been on the hospital shelf prior to its listed 18-month expiration date. This variability in potency made it more difficult to develop a diagnostic test that could accurately detect the presence of FGBD based on measures of GBEF in individuals whose gallbladders had been stimulated by KINEVAC. After Bracco developed the currently marketed KINEVAC formulation, it discontinued the two-ingredient formulation in order to ensure that only the stable and effective formulation was used for CCK-CS diagnostic procedures. Clinical use of the new formulation provided a safe and effective diagnostic, because vials of the more stable formulation contained less variability in potency than vials of the old unstable formulation.

Bracco discontinued the two-ingredient KINEVAC formulation for the additional reason that it produced higher levels of impurities than the currently marketed KINEVAC formulation. Sincalide degradation results in a desulfated sincalide impurity in which the sulfate group on the tyrosine side chain of sincalide is hydrolyzed. In addition to this desulfated sincalide, several

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[11] *See* DiBaise JK, et al. Cholecystokinin-Cholescintigraphy in Adults: Consensus Recommendations of an Interdisciplinary Panel. *Clin. Gastroenterol. Hepatol*. 2011 May; 9 (5): 376-384.

[12] *Id.*

[13] Norenberg, JP, et al. Prescriber Beware: It Is Ill Advised to Administer Compounded Sincalide. *J. Nucl. Med.* 2013 Nov.; 54(1): 23N-24N.

[14] *Id.*at 23N.

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