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December 2, 2013

VIA HAND DELIVERY

Howard Sklamberg, Esq.
Director of Compliance

and

Thomas J. Cosgrove, Esq.
Office Director, Office of Unapproved New Drugs and
Labeling Compliance

United States Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
10903 New Hampshire Avenue
Bldg. 51, Rm. 5271
Silver Spring, MD 20993-0002

Re: NDA No. 022432, H.P. Acthar Gel

Dear Mr. Sklamberg and Mr. Cosgrove:

We write to bring to your attention serious concerns we have with H.P. Acthar Gel® (repository corticotropin injection) ("Acthar Gel"), the subject of New Drug Application No. 022432, sponsored by Questcor Pharmaceuticals, Inc. ("Questcor").

Acthar Gel has been marketed in the United States for a variety of indications since 1952. Questcor purchased the rights to the drug in 2001 for $100,000 and in 2010 secured United States Food and Drug Administration ("FDA" or "the Agency") approval – and an orphan drug designation – for its use in treating infantile spasms.

Herein we report on data and analysis from [redacted] (b) (4), [redacted] (b) (4) contract laboratory that specializes in biopharmaceutical product characterization, analytical testing, and complex biologics characterization services for the pharmaceutical and medical device industries. [redacted] (b) (4) has determined that vials of Acthar Gel it examined contain little or none of the active pharmaceutical ingredient ("API") corticotropin. Instead, [redacted] (b) (4) has found that the vials contain a degraded derivative of corticotropin that is known to lack the same potency as corticotropin.

Based on the results of (b) (4) qualitative and quantitative analyses, it is clear that the Acthar Gel (b) (4) examined is not what Questcor purports it to be. While (b) (4) analyses do not demonstrate why corticotropin is absent from the Acthar Gel – perhaps because Questcor's formulation is inherently unstable and degrades quickly; or because the manufacturing process is poorly controlled or flawed and causes an unwanted chemical reaction; or because the starting material was simply inadequate – (b) (4) findings raise important regulatory concerns about the identity, purity and stability of Questcor's drug product that warrant an FDA investigation.

(b) (4) analyses are significant on their own, but even more so when considered in light of Questcor's own statements regarding the seemingly unknown nature of the active peptide in its Acthar Gel drug product. As explained further below, Questcor itself admits that it does not know what active ingredient is present in Acthar Gel. Because it appears not to be corticotropin, the sole named active ingredient that FDA reviewed and approved, Acthar Gel is by definition an unapproved new drug. And it follows that neither Questcor, nor any other sponsor, has ever presented data on this new drug to FDA concerning the safety or efficacy for the listed indications, including infantile spasms.

The absence of corticotropin in Acthar Gel presents significant health and safety concerns. As FDA has made clear in the drug labeling, physicians must carefully wean patients taking corticotropin at the end of their treatment to allow natural hormone production to resume.[1] That process cannot be well controlled if the dosage of corticotropin delivered in Acthar Gel is not consistent. Further, as to indications and usage, the prescribing information for Acthar Gel provides that the drug product (1) "is . . . indicated as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age;" (2) "is indicated for the treatment of exacerbations of multiple sclerosis in adults;" and (3) "may be used for the following disorders and diseases: rheumatic; collagen; dermatologic; allergic states; ophthalmic; respiratory; and edematous state."[2] Patients suffering from those diseases can suffer long-term negative consequences if their treatment lacks sufficient therapeutic benefit.

The leading indication for Acthar Gel is for infantile spasms.[3] The syndrome typically develops in children under two years of age and is associated with seizures or spasms and marked EEG abnormalities.[4] It results in delayed development, permanent cognitive

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[1] Ex. 1, H.P. Acthar Gel, Highlights of Prescribing Information (issued Sept. 2012) at p. 2.

[2] *Id.* at 1.

[3] *Id.*

[4] Ex. 2, FDA Center for Drug Evaluation and Research, Application No. 022432Orig1s000, Cross Discipline Team Leader Review, Sept. 27, 2010, at p. 2.

impairment, and additional seizure disorders when the infant matures.[5] Fewer than 5% of children diagnosed with it mature to be neurodevelopmentally normal.[6]

When properly dosed, corticotropin is believed to be an effective treatment for infantile spasms, and was used off-label to treat the syndrome for decades before Questcor secured Acthar Gel's approval for the indication. Although other treatments are accepted and available for infantile spasms, including valproic acid, prednisone, and Sabril – the other FDA-approved treatment[7] – corticotropin is considered the treatment of choice by the pediatric neurology community and has been for decades.[8] Patients treated with Acthar Gel, however, may not be getting the proper therapeutic benefit if, as [redacted] (b) (4) data shows, the drug contains little, if any, non-degraded corticotropin.

To protect infants and numerous other patients treated with Acthar Gel that is devoid of corticotropin, we strongly urge FDA to examine Questcor's manufacturing and quality control practices immediately, to determine the extent and cause of the problem and, if necessary, to initiate an appropriate regulatory response to ensure patient safety.

1. Adrenocorticotropic Hormone

Adrenocorticotropic hormone ("corticotropin" or "ACTH")[9] is a single-chain polypeptide comprising 39 amino acids.[10] It is secreted by the anterior pituitary and stimulates the adrenal cortex to produce and secrete cortisol, corticosterone, aldosterone, and a number of weakly androgenic substances.[11] Corticotropin-releasing hormone ("CRH") from the hypothalamus stimulates the release of corticotropin. Cortisol, in the converse, acts via a negative biofeedback mechanism in the serum and decreases the output of corticotropin.[12]

Acthar Gel purportedly contains a highly purified ("H.P.") form of corticotropin derived from pigs and embedded in a 16% gelatin gel, which permits prolonged release after

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[5] *Id.*

[6] *Id.*

[7] *Id.*

[8] *Id.*

[9] Adrenocorticotropic hormone, ACTH and corticotropin can be used interchangeably to describe the approved active ingredient in H.P. Acthar Gel.

[10] Ex. 3, Kamlesh Patel, *Stability of Adrenocorticotropic Hormone (ACTH) and Pathways of Deamidation of Asparaginyl Residue in Hexapeptide Segments* in *Stability and Characterization of Protein and Peptide Drugs: Case Histories* 201, 202-03 (1993).

[11] *Id.*

[12] Ex. 4, Jacob Gettig et al., *H.P. Acthar Gel and Cosyntropin Review, Clinical and Financial Implications*, P&T, Vol. 34 No. 5, May 2009, at 250.

intramuscular or subcutaneous injection.[13] According to the prescribing information, Acthar Gel is marketed as a 5 mL multi-dose vial containing 80 USP units per mL.[14]

(a.) Drug History

(i.) Early Development Efforts

In the 1940s, researchers at the Mayo Institute in Minnesota studied the pharmaceutical properties of hormones made by adrenal glands, the small glands that sit on top of the kidneys that release stress hormones. In the course of that research, Drs. Phillip Hench and Edward Kendall, who together would win the Nobel Prize "for their discoveries relating to the hormones of the adrenal cortex,"[15] discovered that cortisone injections lessened the symptoms of rheumatoid arthritis.[16] Because cortisone was difficult to synthesize and not readily available, Dr. Hench sought an alternative substance to inject into patients to stimulate the body's own production of cortisone.[17] Dr. Hench turned to corticotropin, which Armour Pharmaceutical Company, a subsidiary of the meat-packing giant Armour & Company, had recently isolated from the glands of pigs. Dr. Hench found that patients with rheumatoid arthritis treated with corticotropin experienced favorable results that were comparable to those treated with cortisone. Importantly, corticotropin overcame cortisol's availability issues; corticotropin was readily available as a by-product from Armour's slaughter yards.

Armour developed highly purified corticotropin, which it embedded in a gelatin base to slow the hormone's release after injection. In 1952, Armour secured FDA approval of Acthar Gel to treat a wide range of diseases and disorders, including rheumatoid arthritis "that at the time were thought to benefit from steroid mediated immunosuppression . . . ."[18]

In 1977, FDA significantly narrowed the list of approved indications for Acthar Gel after its review under the Drug Efficacy Study Investigation ("DESI"). The drug continued to be widely used, however, until the 1980s when manufacturers developed new inexpensive steroid treatments, including prednisone and cortisone, which supplanted Acthar Gel as the treatment of choice for rheumatoid arthritis and other common indications.

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[13] Ex. 5, FDA Center for Drug Evaluation and Research, Application No. 022432Orig1s000, Clinical Consultation, May 26, 2010, at p. 1.

[14] Ex. 1, H.P. Acthar Gel Prescribing Information (issued Sept. 2012) at 1.

[15] Ex. 6, http://www.nobelprize.org/nobel_prizes/medicine/laureates/1950/.

[16] Ex. 7, Andrew Pollack, Questcor Finds Profits, at $28,000 a Vial, N.Y. Times, Dec. 29, 2012 at 4.

[17] *Id.*

[18] Ex. 5, FDA Clinical Consultation, May 26, 2010, at p. 1.

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By 1995, Rhône-Poulenc, which had acquired Acthar Gel, decided to discontinue the product altogether, rather than remedy quality control issues FDA had identified at its manufacturing facility.[19] In 1999 Rhône-Poulenc merged with Hoechst AG and became Aventis, and Aventis resumed manufacture of Acthar Gel under pressure from physicians and patient groups who were using the drug product for the off-label treatment of infantile spasms.[20] Sales, however, slipped to less than $1 million per year[21] and rather than continue production, Aventis sold the drug to Questcor in 2001.[22]

(ii.) Questcor's Push for Orphan Drug Designation

After it purchased Acthar Gel, Questcor embarked on a spectacularly successful effort to increase the profitability of what had previously been a low-selling drug.[23] Central to its strategy was its effort to secure FDA approval for an added indication for infantile spasms and an accompanying orphan drug designation. As Don Bailey, Questcor's CEO, would later explain to investors:

> In 2007 we changed our strategy and adopted an orphan business model strategy, and 2007 was then the first time in a 60-year, 55-year history up to then that Acthar actually made money. So it lost money for 55 years and then we changed the strategy and it's been profitable ever since.[24]

In June 2006, Questcor filed a supplemental new drug application ("sNDA") seeking approval to add infantile spasms as an indication for Acthar Gel.[25] Although FDA initially issued a non-approvable letter on May 10, 2007, after a series of amendments to the application, Questcor obtained final approval on October 15, 2010.

FDA also granted Questcor's request for orphan drug status based on the rare rate of occurrence for infantile spasms. That designation ensured Questcor seven years of market exclusivity, through at least October 2017. The designation was particularly valuable to Questcor since it does not have patents that would otherwise protect the decades-old drug from

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[19] Ex. 7, Andrew Pollack, Questcor Finds Profits, at $28,000 a Vial, N.Y. Times, Dec. 29, 2012 at 5..

[20] Ex. 8, David Morrow, Rhône-Poulenc and Hoechst Agree on Start of a Merger, N.Y. Times, Dec. 2, 1998.

[21] Ex. 7, Andrew Pollack, Questcor Finds Profits, at $28,000 a Vial, N.Y. Times, Dec. 29, 2012 at 5.

[22] Ex. 9, Tr. Don Bailey, CEO Questcor Pharmaceuticals, Inc., Presentation at UBS Investment Bank's Global Life Sciences Conference, Sept. 19, 2011 at 1.

[23] *Id.*

[24] *Id.*

[25] Ex. 2, September 27, 2010 FDA Cross-Discipline Team Leader Review at 5.

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generic competition.[26] Questcor has since used its market position to extract substantial premiums on sales of Acthar Gel. Indeed, Questcor has increased the price of the drug an extraordinary 70,000% – from $40 per vial to $28,000 per vial, or more[27] – since it purchased Acthar Gel in 2001.[28]

As Questcor's drug application indicates, the company conducted no new clinical studies to support its sNDA. Due to Acthar Gel's regulatory status that allowed Questcor to piggyback on data submitted to the Agency decades earlier, FDA did not require such studies. Instead, Questcor relied exclusively on investigator-initiated studies that had been conducted decades earlier and years before Questcor manufactured Acthar Gel. Thus, the clinical evidence Questcor submitted and FDA relied on in its grant of approval and orphan drug exclusivity were conducted on a corticotropin-containing drug product that Questcor did not manufacture, and such clinical studies were conducted without participation or investment by Questcor.

Notably, during its statistical review of Questcor's sNDA, FDA expressed concern that "[w]ith such a small sample size, the study sample may not be a good representation of the intended pediatric population. The data to draw a definitive conclusion are limited."[29] Only one of the studies was considered pivotal and the other two were found to be merely supportive.[30] FDA's clinical review also criticized the studies and found that all three "have significant flaws in design and analysis."[31] Nonetheless, despite its expressed concern and admission that the data did "not meet the usual Agency standard for NDA approval,"[32] FDA approved the infantile spasms indication, citing in part the "continued off-label use of Acthar Gel for this indication . . . ."[33]

Questcor's reliance on decades-old testing of a corticotropin-containing product that it did not make is particularly troubling in light of comments Questcor itself has made about the manufacture of its Acthar Gel drug product. For example, the company's Chief Scientific

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[26] Ex. 9, Tr. Don Bailey, CEO Questcor Pharmaceuticals, Inc., Presentation at UBS Investment Bank's Global Life Sciences Conference September 19, 2011 at 2.

[27] The $28,000 per vial price reflects the wholesale price of the product. The end user likely pays thousands of dollars more due to mark-ups by the distributor and pharmacy. In fact, an internet search to purchase Acthar Gel shows an average price above $31,000 per vial. *See* Ex. 10, H.P. Acthar Gel Prices, http://www.goodrx.com/h.p.-acthar, last visited Nov. 7, 2013.

[28] Ex. 7, Andrew Pollack, Questcor Finds Profits, at $28,000 a Vial, N.Y. Times, Dec. 29, 2012 at 5.

[29] Ex. 11, December 10, 2009 FDA Statistical Review and Evaluation at 4.

[30] Ex. 12, September 27, 2010 FDA Medical Clinical Review at 5.

[31] *Id.*

[32] *Id.*

[33] *Id.*

Officer, David Young, told investors in 2012 that "in 2001 and 2003, we took over and acquired Acthar Gel, the modified-release formulation of Acthar. And we changed the manufacturing, modified it, got FDA approval to move forward."[34]

Additionally, Questcor now admits that the Acthar Gel it markets may have additional active ingredients besides corticotropin. Describing Acthar Gel and its mechanism, Mr. Young told investors:

> From those hundreds and hundreds of peptides, we're trying to extract just ACTH. But of course, if you think about it, if I have this mixture and I'm trying to extract only one molecule, that's very unlikely. Instead what you're doing, you're extracting ACTH plus other peptides that are in that mixture . . . . So the question we had in 2008 and 2009 is how many active peptides are really in Acthar, and do they have any meaning? Are they clinically significant? So we've been working on the chemistry trying to identify the peptides. We've been working on the pharmacology, trying to determine which ones are active, which ones are not active. And what we found is that there are multiple peptides in Acthar Gel. These multiple peptides have multiple pharmacological properties. They're not exactly the same. They're not qualitatively exactly the same and they're not quantitatively exactly the same.[35]

These statements suggest that the drug product Questcor markets today is comprised of active ingredients that were not identified in the studies it submitted to FDA to obtain approval for the treatment of infantile spasms. Furthermore, [redacted] (b) (4) data suggests that the active ingredient FDA approved, corticotropin, is present in at most only trace amounts.

Questcor's CEO, Don Bailey has also made statements to investors asserting that the active ingredient in its Acthar Gel is not simply corticotropin:

> It's an undisclosed composition, so that's a trade secret. The manufacturing process is also a trade secret. It's complex, it's unique, and we own all elements of the manufacturing process. We have exclusive worldwide rights to Acthar, so we own it lock, stock and barrel. We have no partners. The composition of Acthar that comes out of the manufacturing process is tied to the process,

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[34] Ex. 13, Tr. of Questcor Presentation at July 13, 2012 JMP Securities Health Care Conference at 4 (emphasis added).

[35] *Id.* at 4-5.

> so if you don't know the process you can't figure out what's actually in Acthar. Acthar is technically a polypeptide, but there are probably multiple active ingredients and there are multiple peptides within Acthar, and they're undisclosed.[36]

Even without (b) (4) recent data finding no corticotropin in tested vials of Acthar Gel, Questcor's own comments as to changes in the manufacturing process and the likely presence of other active peptides merit review and investigation. FDA, of course, requires that an NDA include, among other things, a full list of the components of a drug and statement of its composition.[37] Questcor, however, claims that the 60-year-old drug it is now marketing contains "multiple active ingredients" that were not reviewed and evaluated by FDA. (b) (4) testing confirms that claim, at least to the extent it shows that the drug product Questcor markets appears to be different from the product approved by FDA.

(iii.) Manufacturing

After Questcor purchased the rights to Acthar Gel from Aventis in 2001, it transitioned manufacturing to new contract manufacturers.[38] In June 2005, FDA approved the transfer of the API manufacturing process to BioVectra dcl ("BioVectra") in Charlottetown, Prince Edward Island, Canada.[39] The final fill and packaging is done by Chesapeake Biological Laboratories in Baltimore, Maryland.[40] In January 2013, Questcor announced that it had acquired BioVectra, noting that "[t]he acquisition will enable Questcor to further secure the manufacturing process trade secrets surrounding Acthar."[41]

2. Qualitative and Quantitative Analyses of Acthar Gel Indicate that It Does Not Contain Corticotropin

To investigate the content and character of the active ingredient in Acthar Gel, (b) (4)[42] developed robust analytical test methods and performed cGMP-grade testing on

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[36] Ex. 14, Questcor Corp., Form 8-K at 2 (August 22, 2011) (emphasis added).

[37] 21 U.S.C. § 355(b)(1)(A).

[38] Ex. 15, Questcor Press Release, Questcor Announces FDA Approval of Acthar API Manufacturing Transfer, June 29, 2005.

[39] *Id.*

[40] *Id.*

[41] Ex. 16, Questcor Press Release, Questcor Pharmaceuticals to Acquire BioVectra Inc., January 2, 2013.

[42] (b) (4) specializes in advanced analytical testing in support of biopharmaceutical product characterization. It operates according to FDA current Good Manufacturing Practice regulations and the validation was done in accordance with The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH").

four vials of the drug product. [redacted] (b) (4) test methods, results, and analyses are referenced herein and attached as Exhibits 17-19, 23, 26, and 27. The results of [redacted] (b) (4) testing demonstrate that: (1) Acthar Gel contains deamidated corticotropin; (2) the deamidated corticotropin is present in Acthar Gel at a concentration of approximately 0.21 mg/mL or 16.8 IU/mL; and (3) Acthar Gel does not contain a detectable peak corresponding to non-deamidated corticotropin.[43] These findings raise concerns as to the active peptide in the drug product, including the actual corticotropin concentration in Acthar Gel in view of the 80 IU/mL label claim of the drug product, and the potency required by the United States Pharmacopeia (USP) (80.0-125.0% label claim) for Acthar Gel.[44]

Deamidation is a chemical reaction in which an amide functional group is removed from an organic compound. It can alter the physicochemical and functional characteristics of peptide and protein drugs, such as corticotropin, and deamidation is a known pathway of chemical degradation.[45] As explained in detail below, there is a demonstrated relationship between deamidation and reduced corticotropin biological activity, and thus [redacted] (b) (4) data are indicative of a reduction in Acthar Gel's potency.

(a.) Deamidation Decreases the Potency of Porcine Corticotropin

Porcine corticotropin is a well-characterized 39-amino acid peptide.[46] While porcine corticotropin is referenced as the active ingredient in Acthar Gel, corticotropin derived from other species has been studied, and the first 24 amino acids are conserved among mammals.[47]

The amino acid sequence for porcine corticotropin, depicted below, includes an Asn residue at position 25.[48]

SYSMEHFRWGKPVGKKRRPVKVYPNGAEDELAEAFPLEF

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[43] Ex. 17, [redacted] (b) (4)

[44] Ex. 1, H.P. Acthar Gel Prescribing Information (issued Sept. 2012) at 1; Ex. 20, USP 36 at 3106 (2013). The United States Pharmacopeia ("USP')—the FDA-designated official compendium for drugs—requires 80.0-125.0% potency or 64 IU/mL-96 IU/mL). *See* USP website, http://www.usp.org/about-usp.

[45] *See, e.g.*, Ex. 21, Arthur B. Robinson et al., Controlled Deamidation of Peptides and Proteins: An Experimental Hazard and a Possible Biological Timer, 66 Proceedings of the National Academy of Sciences 753, 753-54; Ex. 22, L. Gráf et al., The Influence of Deamidation on the Biological Activity of Porcine Adrenocorticotropic Hormone (ACTH), 5 Horm. Metab. Res. 142, 142-43 (1973).

[46] Ex. 3, Patel (1993) at 202.

[47] *Id.*

[48] *See, e.g.*, Ex. 23, [redacted] (b) (4)

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The Asn and Gln amino acid residues are known to be unstable due to their propensity to undergo hydrolytic deamidation of their functional side chains.[49] Deamidation of Asn residues is a known chemical pathway for peptide and protein degradation.[50] In corticotropin, the single Asn residue at position 25 is particularly prone to nonenzymatic deamidation.[51] When it deamidates, corticotropin leads to the formation of the α-linked Asp residue, or a mixture of the α-linked Asp residue and a β-linked Asp residue (isoAsp), as shown below.[52]

[49] Ex. 21, Arthur B. Robinson et al., Controlled Deamidation of Peptides and Proteins: An Experimental Hazard and a Possible Biological Timer, 66 Proceedings of the National Academy of Sciences 753, 753 (1970).

[50] *Id.*

[51] *See, e.g.*, Ex. 3, Patel (1993) at 204-06.

[52] Ex. 24, Neelima Bhatt et al., Chemical Pathways of Peptide Degradation. I. Deamidation of Adrenocorticotropic Hormone, 7 Pharmaceutical Research 593, 597 (1990).

Separation of corticotropin from deamidated corticotropin is possible through IEF and cation-exchange HPLC.[53] Yet attempts to separate the two deamidated species – the Asp peptide and the isoAsp peptide – have been unsuccessful.[54]

Deamidation of corticotropin has been shown to be pH-dependent, with deamidation rate increasing with increasing pH in the pH range of 5-12.[55] Additionally, the rate of deamidation of corticotropin has been shown to increase with temperature, following the Arrhenius equation.[56]

Deamidation can result in changes in protein function, and this has been shown specifically for corticotropin.[57] Gráf et al. deamidated porcine corticotropin in 0.1 M ammonia solution at 37° C for six hours, then assayed the corticosteroidogenetic potency of the deamidated peptide in the peripheral blood of laboratory rats after intravenous administration.[58] Gráf et al. found a considerable decrease in the corticosteroidogenetic potency of corticotropin following deamidation, as shown in the below comparison of corticotropin and deamidated corticotropin (referenced as "ACTH" and "DACTH," respectively, in Table 1, below), and the researchers postulated that deamidation was responsible for the decreased biological activity.[59]

Table 1. The biological activity of ACTH before and after deamidation

Peptide		IU/mg
ACTH	(a)	74.8 ± 4.8
ACTH	(b)	91.2 ± 8.5
DACTH	(a)	32.9 ± 2.4
DACTH	(b)	49.0 ± 2.7

Subsequently, Ekman et al. isolated and measured the biological activity of corticotrophic variants of porcine corticotropin.[60] Ekman et al. determined that the fragment "F2" fit corticotropin 7-38, giving the expected amino acid structure up to residue 24, and demonstrating

[53] *Id.* at 596.

[54] *Id.*

[55] Ex. 3, Patel (1993) at 208-09; Ex. 24, Bhatt (1990) at 597-98.

[56] Ex. 3, Patel (1993) at 214-15.

[57] Ex. 22, L. Gráf et al., The Influence of Deamidation on the Biological Activity of Porcine Adrenocorticotropic Hormone (ACTH), 5 Horm. Metab. Res. 142, 142-43 (1973).

[58] *Id.* at 142.

[59] *Id.* at 143.

[60] Ex. 25, R. Ekman et al., Novel variants of adrenocorticotrophic hormone in porcine anterior pituitary, 8 Regulatory Peptides 305, 305-07 (1984).

deamidation at the Asn-Gly structure at position 25-27.[61] This fragment showed reduced corticotrophic activity, as compared to the intact porcine corticotropin 1-39 peptide, as measured by C_{50}, the molar concentration giving 50% of the maximal response, in isolated rat adrenal cells.[62]

(b.) (b) (4) Analytical Testing

In preparation for its analysis, (b) (4) performed method development/validation, and R&D-grade sample testing to generate a polypeptide characterization and amino acid sequencing method to analyze the active ingredient in Acthar Gel by LC/MS/MS. As part of this step, (b) (4) developed a method to (b) (4) the active corticotropin from the 16% gelatin matrix in Acthar Gel by (b) (4), which showed only minimal loss of corticotropin.[63] The complete test method, (b) (4) is attached hereto as Exhibit 26.

Next, (b) (4) performed cGMP-grade sample testing on Acthar Gel, using method (b) (4) The results of the cGMP-grade testing demonstrate that the corticotropin in each Acthar Gel sample contains isoAsp or Asp at position 25, and Glu at position 30, indicative of deamidation of corticotropin in the marketed product.[64]

Building on these qualitative findings, (b) (4) developed a robust LC/MS method to quantify the amount of deamidated corticotropin in the formulated Acthar Gel drug product.[65] The complete test method, (b) (4), is attached hereto as Exhibit 27. In testing for the presence of non-deamidated corticotropin in Acthar Gel by (b) (4) (b) (4) did not find a detectable peak for non-deamidated corticotropin.[66] Next, comparing the concentration of deamidated corticotropin peptide in test samples of Acthar Gel to a standard concentration curve generated from a (b) (4), (b) (4) demonstrated that Acthar Gel contains approximately 0.21 mg/mL deamidated corticotropin.[67]

The methods developed by (b) (4), and the data, results and analyses from (b) (4) testing are discussed in further detail below.

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[61] *Id.* at 309.

[62] *Id.* at 311-12.

[63] Ex. 23, (b) (4)

[64] *See generally* Ex. 18, (b) (4)

[65] Ex. 27, (b) (4) *see* Ex. 28, (b) (4)

[66] Ex. 19, (b) (4)

[67] *Id.* at 28-30.

(c.) (b) (4) Qualitative Analysis Reveals Deamidated Corticotropin in Acthar Gel

(i.) (b) (4) LC/MS/MS Method

(b) (4) developed a robust method to analyze the active peptide in Acthar Gel by LC/MS/MS.[68] The method involves (b) (4) of the peptide in Acthar Gel from the 16% gelatin in which it is formulated, followed by chromatographic separation of the structural isomers of corticotropin using a (b) (4).[69] The method provides reproducible chromatography that can be compared directly to traces observed for corticotropin and deamidated corticotropin controls.[70]

As one control, (b) (4) used porcine corticotropin from (b) (4).[71] The major species in the mass spectrum for the control peptide demonstrates a main peak that elutes at a retention time of approximately 11.5 minutes, and has a mono-isotopic molecular weight of 4564.3 Da (± 0.1 Da).[72] (b) (4) found that the MS/MS spectrum for the (b) (4) gave the most extensive fragmentation and the fragment ions confirmed the amino acid sequence.[73] As a second control, (b) (4) prepared deamidated porcine corticotropin by (b) (4).[74] The mass spectrum for the control deamidated peptide includes a major species that elutes at approximately 12.5 minutes, and has a mono-isotopic molecular weight of 4565.3 Da (± 0.1 Da).[75] (b) (4) found that the MS/MS spectrum for the (b) (4) gave the most extensive fragmentation and the fragment ions confirmed the amino acid sequence, including the presence of deamidation at Asn at position 25.[76]

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[68] Ex. 23, (b) (4).

[69] Ex. 23, (b) (4)

[70] Ex. 23, (b) (4)

[71] Ex. 26, (b) (4); Ex. 29 (b) (4) Certificate of Analysis, Product No. (b) (4), Batch No. (b) (4)

[72] Ex. 26, (b) (4)

[73] Ex. 23, (b) (4)

[74] Ex. 26, (b) (4)

[75] *Id.* at 12.

[76] Ex. 23, (b) (4)

The fragment ion spectra for the controls demonstrate mass shifts corresponding to deamidation in b_{30}^{3+} and b_{33}^{3+}, which have been shown to be diagnostic for deamidated corticotropin.[77]

Theoretical Monoisotopic Masses for Select Fragment Ions			
Non-deamidated ACTH		**Deamidated ACTH**	
y_5^{1+}	505.2657	y_5^{1+}	505.2657
b_{11}^{2+}	705.3246	b_{11}^{2+}	705.3246
b_{30}^{3+}	1177.2685	b_{30}^{3+}	1177.5965
b_{33}^{3+}	1281.6564	b_{33}^{3+}	1281.9844

[77] Ex. 26, (b) (4)

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During method development, [redacted] (b) (4) found that the [redacted] (b) (4) peptide in Acthar Gel produces a two-peak chromatographic profile and a corresponding mass spectrum indicating isobaric peptides, as shown below in part (C).[78]

EXAMPLE: Extracted Ion Chromatograms for (A) [redacted] (b) (4) ACTH, (B) [redacted] (b) (4) Deamidated ACTH and (C) the Test Sample.

[78] Ex. 26, [redacted] (b) (4)

This split profile is consistent with the known Asp and isoAsp isomerizations at position 25 in deamidated porcine corticotropin, and the two deamidation products that would result from deamidation at residue 25.[79]

(ii.) [redacted] (b) (4) Qualitative Analysis Demonstrates Deamidated Corticotropin in Acthar Gel

Using [redacted] (b) (4), as described above, [redacted] (b) (4) analyzed the active peptide in four vials of Acthar Gel first under R&D-grade, and then under cGMP-grade conditions.[80] The data from each study demonstrates the presence of the deamidated corticotropin species in the four vials of Acthar Gel that [redacted] (b) (4) tested.[81]

R&D-Grade Qualitative Analysis

Under R&D testing conditions, [redacted] (b) (4) tested the following four vials of Acthar Gel.[82]

Sample No.	Description[83]	Manufacturer's Lot No.
13-0156-0380	Unopened test sample	1564-61
13-0156-0381	Opened test sample[84]	1564-59
13-0156-0382	Unopened test sample	1564-61
13-0156-0383	Unopened test sample	1564-61

The mass spectral data for each sample of Acthar Gel compare favorably to the standard spectrum for control deamidated porcine corticotropin, rather than control non-deamidated porcine corticotropin.[85] Specifically, the extracted ion chromatograms for each of Sample Nos. 13-0156-0380, 13-0156-0381, 13-0156-0382 and 13-0156-0383 demonstrate the

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[79] Ex. 23, [redacted] (b) (4) *see generally* Ex. 3, Patel (1993) at 203-05.

[80] Ex. 23, [redacted] (b) (4).

[81] Ex. 23, [redacted] (b) (4)

[82] Ex. 17, [redacted] (b) (4)

[83] Sample No. 13-0156-0381 was received by [redacted] (b) (4) previously opened. Upon receipt of all of the samples, including the previously opened sample, [redacted] (b) (4) kept and maintained the samples at cGMP conditions and standards.

[84] [redacted] (b) (4) refers to Sample No. 13-0156-0381 as "opened," as it was opened prior to delivery. Yet, as noted in [redacted] (b) (4), the data collected on this sample was consistent with the data collected on "unopened" Sample Nos. 13-0156-03810, 13-0156-0382 and 13-0156-0383. *See* Ex. 17, [redacted] (b) (4).

[85] *See generally*, Ex. 17, [redacted] (b) (4).

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characteristic two-peak pattern consistent with the known Asp and isoAsp isomerizations at position 25 in deamidated porcine corticotropin.[86]

SAMPLE NO. 13-0156-0380

Fig. 1(A)

Fig. 2(A)

SAMPLE NO. 13-0156-0381

Fig. 3(A)

Fig. 4(A)

SAMPLE NO. 13-0156-0382

Fig. 5(A)

Fig. 6(A)

[86] Ex. 17, (b) (4) at Fig 1(A) (Sample No. 13-0156-0380, sample 1), Fig. 2(A) (Sample No. 13-0156-0380, sample 2); Fig. 3(A) (Sample No. 13-0156-0381, sample 1), Fig. 4(A) (Sample No. 13-0156-0381, sample 2), Fig. 5(A) (Sample No. 13-0156-0382, sample 1); Fig. 6(A) (Sample No. 13-0156-0382, sample 2); Fig. 7(A) (Sample No. 13-0156-0383, sample 1); Fig. 8(A) (Sample No. 13-0156-0383, sample 2); *see generally* Ex. 3, Patel (1993) at 203-05.

SAMPLE NO. 13-0156-0383

Fig. 7(A)

Fig. 8(A)

Additionally, the mono-isotopic masses for the b_{30}^{3+} and b_{33}^{3+}, for each of Sample Nos. 13-0156-0380, 13-0156-0381, 13-0156-0382 and 13-0156-0383, compare favorably with the mass shifts demonstrated in the deamidated corticotropin control.[87]

cGMP-Grade Qualitative Analysis

The data from the cGMP-grade testing are consistent with (b) (4) findings in the R&D-grade analysis. In the cGMP-grade qualitative analysis, (b) (4) samples of Acthar Gel from four vials by LC/MS/MS pursuant to (b) (4), and compared the drug products to (b) (4) non-deamidated corticotropin and (b) (4) deamidated corticotropin controls.[88]

Under cGMP testing conditions, (b) (4) analyzed the same four vials of Acthar Gel: Samples Nos. 13-0156-0380, 13-0156-0381, 13-0156-0382 and 13-0156-0383.[89] Again, (b) (4) determined that the mass spectral data for each sample of Acthar Gel compare favorably to the standard spectrum for control deamidated porcine corticotropin, rather than control non-deamidated porcine corticotropin.[90] Specifically, the extracted ion chromatograms for each of Sample Nos. 13-0156-0380, 13-0156-0381, 13-0156-0382 and 13-0156-0383

[87] Ex. 17, (b) (4) at Fig 1(P)-(Q) (Sample No. 13-0156-0380, sample 1), Fig. 2(P)-(Q) (Sample No. 13-0156-0380, sample 2); Fig. 3(P)-(Q) (Sample No. 13-0156-0381, sample 1), Fig. 4(P)-(Q) (Sample No. 13-0156-0381, sample 2), Fig. 5(P)-(Q) (Sample No. 13-0156-0382, sample 1); Fig. 6(P)-(Q) (Sample No. 13-0156-0382, sample 2); Fig. 7(P)-(Q) (Sample No. 13-0156-0383, sample 1); Fig. 8(P)-(Q) (Sample No. 13-0156-0383, sample 2).

[88] Ex. 18, (b) (4)

[89] *Id.* at 4.

[90] *Id.* at 6, Figs. 1-8.

demonstrate the characteristic two-peak pattern consistent with the known Asp and isoAsp isomerizations at position 25 in deamidated porcine corticotropin.[91]

SAMPLE NO. 13-0156-0380

Fig. 1(A)

Fig. 2(A)

Fig. 3(A)

SAMPLE NO. 13-0156-0381

Fig. 4(A)

Fig. 5(A)

Fig. 6(A)

SAMPLE NO. 13-0156-0382

Fig. 7(A)

Fig 8(A)

Fig. 9(A)

[91] Ex. 18, (b) (4) at Fig 1(A) (Sample No. 13-0156-0380, sample 1), Fig. 2(A) (Sample No. 13-0156-0380, sample 2); Fig. 3(A) (Sample No. 13-0156-0380, sample 3), Fig. 4(A) (Sample No. 13-0156-0381, sample 1), Fig. 5(A) (Sample No. 13-0156-0381, sample 2); Fig. 6(A) (Sample No. 13-0156-0381, sample 3); Fig. 7(A) (Sample No. 13-0156-0382, sample 1); Fig. 8(A) (Sample No. 13-0156-0382, sample 2); Fig. 9(A) (Sample No. 13-0156-0382, sample 3); Fig. 10(A) (Sample No. 13-0156-0383, sample 1); Fig. 11(A) (Sample No. 13-0156-0383, sample 2); Fig. 12(A) (Sample No. 13-0156-0383, sample 3); *see generally* Ex. 3, Patel (1993) at 203-05.

SAMPLE NO. 13-0156-0383

Fig. 10(A)

Fig. 11(A)

Fig. 12(A)

Additionally, the mono-isotopic masses for the b_{30}^{3+} and b_{33}^{3+}, for each of Sample Nos. 13-0156-0380, 13-0156-0381, 13-0156-0382 and 13-0156-0383, compare favorably with the mass shifts demonstrated in the deamidated corticotropin control.[92]

(b) (4) also found in this analysis that the signals for non-deamidated corticotropin could not be detected.[93]

Accordingly, (b) (4) has demonstrated that each of the four vials of Acthar Gel contain the deamidated corticotropin species, and the corticotropin in each vial has the same amino acid sequence as deamidated corticotropin (b) (4), with isoAsp or Asp at position 25.[94]

(d.) (b) (4) Quantitative Analysis Demonstrates Reduced Corticotropin Concentration in Acthar Gel

(i.) (b) (4) Quantitative Analysis Method and Method Development

Building on the qualitative analysis, where only deamidated corticotropin could be detected, (b) (4) developed an LC/MS method to determine the quantity of deamidated corticotropin peptide in Acthar Gel.[95] (b) (4) method for quantitative analysis measures deamidated corticotropin in a sample using a standard curve generated from (b) (4)

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[92] Ex. 18, (b) (4) at Fig 1(P)-(Q) (Sample No. 13-0156-0380, sample 1), Fig. 2(P)-(Q) (Sample No. 13-0156-0380, sample 2); Fig. 3(P)-(Q) (Sample No. 13-0156-0380, sample 3), Fig. 4(P)-(Q) (Sample No. 13-0156-0381, sample 1), Fig. 5(P)-(Q) (Sample No. 13-0156-0381, sample 2); Fig. 6(P)-(Q) (Sample No. 13-0156-0381, sample 3); Fig. 7(P)-(Q) (Sample No. 13-0156-0382, sample 1); Fig. 8(P)-(Q) (Sample No. 13-0156-0382, sample 2); Fig. 9(P)-(Q) (Sample No. 13-0156-0382, sample 3); Fig. 10(P)-(Q) (Sample No. 13-0156-0383, sample 1); Fig. 11(P)-(Q) (Sample No. 13-0156-0383, sample 2); Fig. 12(P)-(Q) (Sample No. 13-0156-0383, sample 3).

[93] Ex. 18, (b) (4)

[94] Ex. 17, (b) (4)

[95] Ex. 19, (b) (4)

(b) (4) [redacted] (b) (4) [redacted].[96] During method development, [redacted] (b) (4) demonstrated the method. [redacted] (b) (4) to be reproducible.[97]

To generate the concentration curve, [redacted] (b) (4) [redacted] [101] Accordingly, [redacted] (b) (4) determined that a standard curve generated from [redacted] (b) (4) [redacted] could be used to quantify corticotropin and deamidated corticotropin.[102]

For method development in the quantitative analysis, [redacted] (b) (4) determined the most abundant charge state and isotopic peaks without overlap for the [redacted] (b) (4) [redacted]

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[96] Ex. 27, [redacted] (b) (4)

[97] Ex. 19, [redacted] (b) (4).

[98] Ex. 27. [redacted] (b) (4)

[99] *Id.* at 4, 6.

[100] *Id.* at 10-14.

[101] Ex. 19, [redacted] (b) (4)

[102] *Id.* at 9, 21.

[103] Ex. 27, [redacted] (b) (4)

[104] Ex. 23, [redacted] (b) (4)

[105] Ex. 19, [redacted] (b) (4)

(b) (4) To quantify the amount of deamidated corticotropin in samples, (b) (4) obtained EICs for each isotopic peak, the peaks were integrated to obtain peak areas, and the areas were used to construct the standard concentration curve.[108]

(b) (4)

(b) (4) also assessed the accuracy of the method by quantifying the amount of corticotropin peptide in (b) (4) then calculated the concentrations of the QC Samples by linear regression, finding that the determined concentrations are 89% and 96%, respectively, demonstrating the accuracy of the method.[113]

During method development, (b) (4) quantified the amount of deamidated corticotropin in Acthar Gel (CSTN 13-0156-0381).[114] (b) (4)

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[106] *Id.* at 10, Fig. 1C.

[107] *Id.* at 9-10, Figs. 1D-I.

[108] *Id.* at 11.

[109] *Id.* at 15-18.

[110] *Id.* at 16.

[111] Ex. 19, (b) (4)

[112] *Id.* at 18.

[113] *Id.* at 18-19.

[114] *Id.* at 20-22.

[115] *Id.* at 6.

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corticotropin in the Acthar Gel samples from the standard curve using linear regression.[116] (b) (4) determined that the concentration of deamidated corticotropin in Acthar Gel (CSTN 13-0156-0381)[117] was approximately 0.1 mg/mL.[118] These results were obtained based on two Acthar Gel sample preparations (b) (4) found that the concentrations varied by 11% between samples, indicating that this is a reproducible method for determining the concentration of deamidated corticotropin in Acthar Gel.[119]

Given the earlier quantitative analysis, the concentration of deamidated corticotropin was less than expected, and (b) (4) analyzed whether the low concentration was due to peptide loss during the (b) (4)[120] (b) (4) and found that the peak area ratios of the (b) (4) vary by 16% in the precipitated and non-precipitated samples.[121] This confirmed that the (b) (4) does not result in large losses of the peptide.[122] Moreover, these results demonstrate that (b) (4) does not account for the reduced concentration of deamidated corticotropin.[123]

Additionally, (b) (4) tested for the presence of non-deamidated Asn in the test samples (Acthar Gel, CSTN 13-0156-0381).[124] (b) (4) found no detectable peak area in the (b) (4) a peak that is diagnostic for the presence of non-deamidated corticotropin.[125]

(ii.) (b) (4) Quantitative Analysis Fails To Detect the Presence of Corticotropin and Demonstrates Approximately 0.21 mg/mL Deamidated Corticotropin in Acthar Gel

(b) (4)

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[116] *Id.* at 20.

[117] Sample No. 10-0156-0381 was the vial that had been opened prior to receipt by (b) (4).

[118] Ex. 19, (b) (4)

[119] *Id.* at 20-21.

[120] *Id.* at 23-24.

[121] *Id.* at 23-24.

[122] *Id.* at 23.

[123] *Id.* at 23.

[124] Ex. 19, (b) (4)

[125] *Id.* at 25, Fig. 10.

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(b) (4) quantified the concentration of deamidated corticotropin peptide (b) (4) determined that the quantitative method is accurate by running (b) (4) QC Samples, and finding that the QC Samples were all within 15% of the expected concentration value.[130]

(b) (4) samples of three Acthar Gel vials.[131] (b) (4) for each of the test samples, and found that the samples do not contain detectable levels of non-deamidated Asn.[132] Quantifying the amount of deamidated corticotropin in the samples, as shown below, (b) (4) found that the average deamidated corticotropin concentration was 0.21 mg/mL (range 0.15-0.27 mg/mL).[133]

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[126] These three samples were vials that were unopened upon receipt by (b) (4)

[127] Ex. 19, (b) (4)

[128] *Id.* at 25-26.

[129] *Id.* at 25-27.

[130] *Id.* at 27-28.

[131] *Id.* at 28-29.

[132] *Id.* at 28, 30, Fig. 14 (top panels).

[133] Ex. 19, (b) (4)

Table 14. Peak Areas and concentration of test samples.

Sample	Test Sample (b) (4) Peak Area	Heavy ACTH (Asp) (b) (4) (b) (4) Peak Area	Test Sample Peak Area /Heavy ACTH (Asp) (b) (4) Ratio	Test Sample Conc. (mg/mL)
13-0156-0380_1	1159647	451371	2.57	0.21
13-0156-0380_2	795019	431510	1.84	0.15
13-0156-0380_3	976102	354292	2.76	0.22
13-0156-0380 Average			**2.39**	**0.19**
13-0156-0382_1	1373108	505185	2.72	0.22
13-0156-0382_2	1126052	449069	2.51	0.20
13-0156-0382_3	781927	229349	3.41	0.27
13-0156-0382 Average			**2.88**	**0.23**
13-0156-0383_1	887684	334934	2.65	0.21
13-0156-0383_2	671165	336455	1.99	0.16
13-0156-0383_3	609297	223146	2.73	0.22
13-0156-0383 Average			**2.46**	**0.20**

In sum, therefore, (b) (4) qualitative and quantitative analyses have demonstrated that: (1) Acthar Gel contains deamidated corticotropin; (2) deamidated corticotropin is present in Acthar Gel at a concentration of approximately 0.21 mg/mL; and (3) Acthar Gel does not contain a detectable peak corresponding to non-deamidated corticotropin.

3. Health Risks

(b) (4) has shown that Acthar Gel contains deamidated corticotropin, and the tested Acthar Gel samples contain approximately 0.21 ml/mL deamidated corticotropin and fail to demonstrate a peak diagnostic for the presence of non-deamidated corticotropin (the only approved active ingredient in Acthar Gel).[134] The reduction in potency of deamidated porcine corticotropin has been well-established.[135] Moreover, Voigt et al. demonstrated that variants of porcine corticotropin are less active than the full 39-amino acid peptide in bioassays.[136] (b) (4) findings thus raise concerns regarding the potency of Acthar Gel, changes in the physiochemical and functional properties of the active ingredient in Acthar Gel, changes in the

[134] Ex. 17, (b) (4)

[135] *See, e.g.*, Ex. 22, Gráf (1973) at 142-43; Ex. 26, Ekman (1984) at 311-12.

[136] Ex. 30, Karlheinz Voigt et al., Isolation and full structural characterization of six adrenocorticotropin-like peptides from porcine pituitary gland: identification of three novel fragments of adrenocorticotropin and of two forms of novel adrenocorticotropin-like peptide, 194 Eur. J. Biochem. 225, 230 (1990).

stability of the active ingredient in the drug product, and immunogenicity issues that FDA may not have considered given Acthar Gel's unique regulatory approval pathway.[137]

4. Statutory and Regulatory Violations

The research data described above suggests several significant violations of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act") that would merit a robust regulatory response.

(a.) Questcor's Acthar Gel Product, as Marketed, Is an Unapproved New Drug

No person may introduce or deliver into interstate commerce any new drug unless FDA has approved an application for such drug in accordance with Section 505 of the FDCA.[138]

As explained above, FDA's 2010 approval of Acthar Gel was based on three clinical studies that evaluated the effectiveness of corticotropin for treatment of infantile spasms. The studies were performed in 1983, 1994, and 1996 – well before Questcor acquired Acthar Gel and began manufacturing the drug itself.[139] Indeed, FDA expressed concern in its review of the application that the drug used in the studies was not the marketed version.[140] Nonetheless, FDA granted approval because the studies suggested that corticotropin offered superior therapeutic results to prednisone in the treatment of infantile spasms.[141]

FDA's approval was specific to repository corticotropin injection as that substance is defined by the official USP monograph. The product that Questcor is manufacturing and marketing today, however, does not conform to the compendial definition, and thus it is not what FDA approved based on a finding of safety and efficacy.

To our knowledge, Questcor has not presented clinical evidence that deamidated corticotropin is safe or effective for the treatment of infantile spasms, nor are we aware of any general recognition of such safety or efficacy. Curiously, Questcor itself has acknowledged the presence of numerous other ingredients, which it claims have therapeutic properties, but it has not identified those ingredients, and we are not aware of any evidence supporting such claims.

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[137] *See generally*, Ex. 31, Darrell The-Yung Liu, *Deamidation: a source of microheterogeneity in pharmaceutical proteins*, 10 TIBTECH 364, 366 (1992).

[138] 21 U.S.C. § 355. *See also* 21 U.S.C. § 301(d) (prohibiting "[t]he introduction or delivery for introduction into interstate commerce of any article in violation of section . . . 505").

[139] Ex. 2, September 27, 2010, FDA Cross-Discipline Team Leader Review at p. 4-6.

[140] Ex. 32, April 5, 2010, FDA Action Memo for NDA 22-432 for the use of H.P. Acthar Gel (repository corticotrophin (sic) injection) in the treatment of Infantile Spasms (IS) at 1.

[141] Ex. 2, September 27, 2010, FDA Cross-Discipline Team Leader Review at p. 4.

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In the absence of clinical evidence supporting an approved new drug application for deamidated corticotropin or the other purported components in Acthar Gel, it is an unapproved new drug.

(b.) Questcor's Acthar Gel Product Is Adulterated

Drugs manufactured in facilities or under conditions that do not comply with current Good Manufacturing Practice ("cGMP") regulations are adulterated within the meaning of the Act.

The cGMP regulations require manufacturers to ensure that products they make conform to specification. For example, manufacturers must have in place production and control procedures designed to assure that the drug products they produce have the identity, strength, quality and purity they are represented to possess.[142] They must have in-process control procedures to monitor the output and to validate the performance of those manufacturing processes that are responsible for causing variability in the characteristics of in-process material and the drug product. They must test in-process material for identity, strength, quality and purity as appropriate.[143] They must test each batch of drug product to ensure conformance to final specifications, including the identity and strength of each active ingredient, and they must reject batches that do not conform.[144] They also must maintain reserve samples of each distributed batch of product and conduct stability testing to ensure their products do not degrade and continue to conform to specifications within the designated expiration dates under appropriate storage conditions.[145]

In addition to following appropriate control procedures, drug manufacturers must document compliance with these procedures in master production, batch production, and control records.[146] Those records must, among other things, document that each significant step in the manufacture, processing, packing or holding of a batch is accomplished, and that each batch conforms with specifications and complies with all in-process and laboratory controls.[147]

(b) (4) test results described above suggest that Questcor's manufacturing facilities are not operating in a good state of control, and that perhaps due to failure to comply with one or more of the cGMP regulations, it is allowing product that does not comply with specifications to be released to the market. Such product is adulterated within the meaning of

[142] 21 C.F.R. § 211.101.

[143] 21 C.F.R. § 211.110.

[144] 21 C.F.R. § 211.165.

[145] 21 C.F.R. §§ 211.166 & 211.170.

[146] 21 C.F.R. §§ 211.186 & 211.188.

[147] 21 C.F.R. § 211.188.

Section 501 of the Act and poses risks to patients who are being treated with a drug that likely will not deliver the desired therapeutic benefit.

(c.) Questcor's Acthar Gel Product Is Misbranded

A drug is misbranded within the meaning of Section 502 of the Act "unless its label bears, to the exclusion of any other nonproprietary name . . . the established name . . . of the drug . . . ."[148] The established name of Acthar Gel, and the name which it bears on its labeling, is repository corticotropin injection.[149] To satisfy the labeling requirements, however, Acthar Gel must have "the identity prescribed for [repository corticotropin injection] in an official compendium."[150]

The official USP monograph identifies repository corticotropin injection as "corticotropin in a solution of partially hydrolyzed gelatin. Its potency is not less than 80.0 percent and not more than 125.0 percent of the potency stated on the label in USP Corticotropin Units."[151] The label for Acthar Gel says it contains "80 USP units per mL."[152] Thus, to comply with the USP monograph – and be properly labeled as repository corticotropin injection – it must contain between 64 (80%) and 100 (125%) units of corticotropin.

In fact, Acthar Gel contains far less than 64 units of corticotropin; indeed, it appears not to contain any corticotropin at all.[153] It is not, therefore, repository corticotropin injection, as defined by the USP and as represented in its labeling, and thus it is misbranded in violation of Section 502 of the Act.

This is a significant violation. As explained above, it is well recognized in current literature that when corticotropin is deamidated, it loses much of its potency.[154] It is therefore hard to say what, if any, therapeutic value Acthar Gel can have, since it seems to contain so little of the active ingredient that was the basis for FDA's approval.

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[148] 21 U.S.C. § 352(e)(1)(A)(i). *See also* 21 U.S.C. § 301(a) (prohibiting "[t]he introduction or delivery for introduction into interstate commerce of any . . . drug . . . that is . . . misbranded").

[149] Ex. 1, H.P. Acthar Gel Package Insert at 1.

[150] 21 C.F.R. § 299.5(b).

[151] Ex. 20, USP 36 at. 3106 (2013).

[152] Ex. 1, H.P. Acthar Gel prescribing information (issued Sept. 2012) at 1.

[153] *See* discussion, *supra*, at 23-24 (citing Ex. 18, TR13-0234 Rev001 at 6; Ex. 19, TR13-0242 Rev001 at 25, 28, 30).

[154] *See* discussion, *supra*, at 9-12 (citing Ex. 22, Gráf (1973) at 142-43; Ex. 25, Ekman (1984) at 311-12).

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(d.) Orphan Drug Status

The orphan drug designation FDA granted Questcor for Acthar Gel is cause for added concern in this case. Very little of Questcor's sales of Acthar Gel are for treatment of infantile spasms – Questcor estimates about 10% of total sales.[155] The vast majority of its sales are for other indications, namely multiple sclerosis and nephrotic syndrome, which would not have supported an orphan drug designation.[156] Because of the orphan drug status, Questcor will enjoy seven years of market exclusivity – until October 2017.[157] During that time, other manufacturers, who might deliver a corticotropin product that conforms to the USP monograph, will be barred from the market.

Questcor has an obligation to patients suffering from infantile spasms to deliver a product that contains the pharmaceutical ingredient that others have shown delivers therapeutic benefit. If it cannot or will not do so, and instead continues to distribute a product that differs from the product described in its application for approval, FDA should consider revoking the orphan drug status and opening the marketplace to competition.

5. <u>Pricing</u>

Before Questcor purchased the rights to Acthar Gel in 2001, it was used primarily off-label for the treatment of infantile spasms and sold for approximately $40 per vial.[158] After Questcor acquired the rights, it immediately raised the price to about $700 per vial, and continued to increase the price until it reached $1,650 per vial in 2007.[159]

In August of 2007 Questcor announced that it was implementing a new business model that would significantly increase the price for Acthar Gel – raising it to $23,000 per vial, a thirteen-fold increase.[160] This "orphan business model strategy" has worked for Questcor and, according to its CEO, "2007 was then the first time in a 60-year, 55-year history up to then that

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[155] Ex. 33, November 13-14, 2013, Questcor Presentation, Credit Suisse Healthcare Conference at 6-7.

[156] *Id.* at 6, showing Q3 2103 sales for nephrology (30-35%), multiple sclerosis (25-30%), rheumatology (20-25%) and other (~2%).

[157] Ex. 34, Acthar Gel Electronic Orange Book Listing, found at http://www.accessdata.fda.gov/Scripts/cder/ob/docs/patexclnew.cfm?Appl_No=008372&Product_No=008&table1=OB_Rx (last visited 2013). Sales for indications other than infantile spasms account for approximately 90% of Acthar's sales.

[158] Ex. 35, Andrew Pollack, Questcor Pays $135 Million to Acquire Rights to a Competitor's Drug, N.Y. Times, June 14, 2013 at 2.

[159] *Id.*

[160] Ex. 36, Karl Stark, Drugs price up more than $21,000; The hike for H.P. Acthar, which treats a rare childhood disorder, has sparked debate over prescription costs, Philadelphia Inquirer, October 2, 2007 at 1.

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Acthar actually made money."[161] However, as discussed above, Questcor's "orphan strategy" actually focuses on marketing the drug for indications other than infantile spasms for which the effectiveness of Acthar Gel has never been established and was not presented to FDA. Nonetheless, Questcor has continued to increase the price of Acthar Gel, despite outcry from doctors and patient groups.[162] A recent internet inquiry returned prices of over $31,000 per vial.[163]

In addition to the market exclusivity Questcor received from its orphan drug designation, it is also actively keeping competition off of the market so it can continue to charge a premium for Acthar Gel. Synacthen® (cosyntropin) is a synthetic peptide consisting of the first 24 amino acids of the 39-amino-acid corticotropin peptide and has similar activity.[164] Owned by Novartis, Inc., it is available in forty countries outside the U.S. and represented a significant threat to Questcor's continued exclusivity if approved for marketing in the U.S.[165] In June 2013, Questcor announced that it had purchased the rights to market Synacthen in the U.S. subject to FDA approval.[166] Questcor outbid a start-up company, Retrophin, that had been negotiating with Novartis to acquire Synacthen and planned to undercut Acthar Gel and sell the synthetic drug for only a few hundred dollars a vial.[167] Questcor paid at least $135 million for the marketing rights, including an initial $60 million payment – far outbidding the $16 million Retrophin was offering upfront; however, Retrophin was offering a sales royalty that could have potentially exceeded the price Questcor will pay.[168] Questcor's acquisition of Synacthen, when approved in the U.S., will guarantee Questcor can continue to charge exorbitant prices for Acthar Gel as well as price

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[161] Ex. 9, Tr. Don Bailey, CEO Questcor Pharmaceuticals, Inc., Presentation at UBS Investment Bank's Global Life Sciences Conference September 19, 2011, at 1.

[162] *See e.g.*, Ex. 7, Andrew Pollack, Questcor Finds Profits, at $28,000 a Vial, N.Y. Times, Dec. 29, 2012; *See* Ex. 36, Karl Stark, Drugs price up more than $21,000; The hike for H.P. Acthar, which treats a rare childhood disorder, has sparked debate over prescription costs, Philadelphia Inquirer, October 2, 2007; Ex. 37, Infantile Spasms Community Newsletter.

[163] Ex. 10, H.P. Acthar Gel Prices, http://www.goodrx.com/h.p.-acthar, last visited Nov. 7, 2013.

[164] Ex. 4, Gettig et al., H.P. Acthar Gel and Cosyntropin Review, Clinical and Financial Implications, P&T, Vol. 34 No. 5, May 2009 at 250.

[165] Ex. 35, Andrew Pollack, Questcor Pays $135 Million to Acquire Rights to a Competitor's Drug, N.Y. Times, June 14, 2013.

[166] Ex. 38, Questcor Press Release, Questcor Pharmaceuticals Acquires Rights to Synacthen®, June 11, 2013.

[167] Ex. 35, Andrew Pollack, Questcor Pays $135 Million to Acquire Rights to a Competitor's Drug, N.Y. Times, June 14, 2013.

[168] *Id.*

Synacthen at a higher price and exclude competition. It now appears that the Federal Trade Commission is investigating Questcor's acquisition of Synacthen.[169]

6. Conclusion

FDA's drug approval process is predicated on the principle that sponsors of new drug applications will come forth with specific, identifiable active pharmaceutical ingredients, formulated to particular specifications, and demonstrate their safety and efficacy for treating particular indicated diseases.

The available evidence suggest that Questcor has turned that process on its head with Acthar Gel. The product it seems to be manufacturing is not the product it described in its application for approval for a new indication, nor is it the product FDA originally approved in 1952. And Questcor's Acthar Gel is not the drug product used in studies that purport to show its therapeutic benefit for infantile spasms, an indication that Questcor has estimated to represent less than 10% of total sales.

Drug manufacturers have an obligation to ensure that the drugs they make conform to the specifications established in their applications. If their products do not conform, neither FDA, treating physicians, nor patients can know that marketed drugs are safe and will deliver the desired benefit. We are concerned, based on the evidence reported here, that Questcor is not meeting that obligation with Acthar Gel, and therefore strenuously urge the Agency to investigate.

If you have any questions about (b) (4) findings or the test methods it used, we would be more than happy to answer them. Please do not hesitate to contact me with any such questions and we will endeavor to get you answers immediately.

Thank you for your time and attention to this problem.

Sincerely,

John H. Fuson

Enclosures

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[169] Ex. 39, Nov. 25, 2013 Citron Research Report, FTC Investigates Questcor: Serious Jeopardy for Synthacthen Deal, available at http://www.citronresearch.com/wp-content/uploads/2013/11/Questcor-and-the-FTC-final1.pdf (last visited Dec. 2, 2013).