September 19, 2019

Victoria Scott
Director, Quality and Regulatory Affairs
Hemispherx Biopharma, Inc.
860 N .Orange Ave., Suite B
Orlando, FL 32801

Dear Ms. Scott:

We are in receipt of your submission dated May 14, 2018, and additional submissions dated March 19, 2019 and April 12, 2019. Your May 14, 2018 submission concerned the export of Ampligen® (rintatolimod), intended for the treatment of severe Chronic Fatigue Syndrome, to Argentina under section 802(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act or Act) [21 U.S.C. § 382(b)(2)]. In support of this export, Hemispherx Biopharma, Inc. (Hemispherx) submitted the following documents to the U.S. Food and Drug Administration (FDA or Agency)[1]:

1. Marketing Authorization Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT)[2] Disposition #9358 (May 14, 2018 submission, Attachment 1).
2. Prospecto Julio 2016 – ANMAT Approved Package Insert (May 14, 2018 submission Attachment 2).
3. Ampligen 9 Informe Julio 2016 VF – ANMAT Approved Pharmaceutical Product Technical-Scientific Report (May 14, 2018 submission, Attachment 3).
4. ANMAT Approved Specifications for rintatolimod (May 14, 2018 submission, Attachment 4).
5. ANMAT Approved Label (May 14, 2018 submission, Attachment 5).
6. ANMAT Disposition 6677/10, “Regulatory Guideline for Good Clinical Practices in Clinical Pharmacology Studies” (March 19, 2019 submission).
7. Decree No. 150/1992, “Rules for the registration, manufacture, fractionation, prescription, distribution, marketing, export and import of medicinal products” (April 12, 2019 submission).
8. ANMAT Disposition 5358/2012 (guidelines for Good Pharmacovigilance Practice) (April 12, 2019 submission).

[1] FDA is basing its determinations on the translated documents provided by Hemispherx; FDA has not conducted additional searches or translations to determine if the documents and translations provided by Hemispherx are correct, complete, and current. References to Argentinian regulatory requirements in this document refer to the translations submitted by Hemispherx. If FDA later has reason to believe that these translations are, in any material way, incorrect, incomplete, or outdated, FDA will take the necessary steps to amend or revoke its determinations. FDA may also pursue other remedies as it deems appropriate.

[2] ANMAT, the National Administration of Drugs, Food and Medical Technology, is responsible for pharmaceutical regulation in Argentina.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

In addition, FDA received from ANMAT a translation of ANMAT Disposition 3602/2018 and of ANMAT's "Good Manufacturing Practices for Manufacturers, Importers/Exporters of Drugs of Human Use," which establishes a standard for current human drug good manufacturing practices (CGMP) (hereinafter referred to as "ANMAT CGMP Standard").[3]

I. Introduction

Pursuant to section 802(b)(2) of the FD&C Act, an unapproved drug may be directly exported to a country that is not listed in section 802(b)(1)(A) of the Act, if the following criteria are met:

- The drug complies with the laws of the country to which it would be exported and has a valid marketing authorization by the responsible authority in that country (see 21 U.S.C. § 382(b)(2)(A));
- FDA determines that all of the following requirements are met in that country[4]:
    - There are statutory or regulatory requirements which require the review of the drug for safety and effectiveness by an entity of the government of the country, and which authorize the approval of only those drugs which have been determined to be safe and effective by experts employed by or acting on behalf of such entity and qualified by scientific training and experience to evaluate the safety and effectiveness of drugs on the basis of adequate and well-controlled investigations, including clinical investigations, conducted by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs (see 21 U.S.C. § 382(b)(2)(B)(i));
    - There are statutory or regulatory requirements that the methods used in, and the facilities and controls used for the manufacture, processing, and packing of drugs in the country are adequate to preserve their identity, quality, purity, and strength (see 21 U.S.C. § 382(b)(2)(B)(ii));
    - There are statutory or regulatory requirements for the reporting of adverse reactions to drugs and procedures to withdraw approval and remove drugs found not to be safe and effective (see 21 U.S.C. § 382(b)(2)(B)(iii));
    - There are statutory or regulatory requirements that the labeling and promotion of drugs must be in accordance with the approval of the drug (see 21 U.S.C. § 382(b)(2)(B)(iv)); and
- The requirements of section 802(f) of the Act [21 U.S.C. § 382(f)] are met.

[3] ANMAT approved its CGMP standard through Disposition No. 3602/2018. *See* ANMAT Disposition 3602/2018 at Section 1.

[4] An FDA determination that the requirements listed in section 802(b)(2)(B)(i)-(iv) [21 U.S.C. § 382(b)(2)(B)(i)-(iv)] are met in a country is a limited determination and does not apply beyond export under section 802 of the Act. For example, an "802(b)(2)(B) determination" is not a finding of "equivalence" between the importing country and the United States (or any other country). In addition, an 802(b)(2)(B) determination does not constitute a determination about whether an unapproved drug meets any criterion for approval under U.S. laws.

II. Requirements of Section 802(b)(2)(A)

Section 802(b)(2)(A) of the FD&C Act [21 U.S.C. § 382(b)(2)(A)] imposes two conditions on the export of an unapproved drug to an unlisted country. First, the drug must comply with the laws of the country to which it is being exported; second, the drug must have a valid marketing authorization in that country. It is the exporter's responsibility, here, Hemispherx, to ensure that each shipment complies with these conditions. FDA, however, does recommend that firms intending to export drugs under section 802(b)(2) of the Act provide documentation to FDA showing that the drug complies with the foreign country's laws and has a valid marketing authorization. *See* Guidance for Industry: Exports Under the FDA Export Reform and Enhancement Act of 1996, July 23, 2007, Section VII.F. We acknowledge that, according to the marketing authorization certificate included in your submission, the responsible authority for issuing marketing authorizations for drugs in Argentina resides in ANMAT, and ANMAT has issued a marketing authorization for the pharmaceutical product Ampligen® (rintatolimod) to be imported and distributed in Argentina by the United States manufacturer, Hemispherx. *See* Marketing Authorization Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT) Disposition #9358 (May 14, 2018 submission) (Attachment 1). We also acknowledge your affirmation that rintatolimod complies with the laws of Argentina, the country to which it will be exported. *See* Victoria Scott, Hemispherx Notification of Shipment to Argentina of Ampligen: ANMAT Marketing Authorization Certificate Number 9358 (May 14, 2018).

III. Requirements of Section 802(b)(2)(B)

Section 802(b)(2)(B) describes four components of a drug regulatory system that must be provided for in the statutes or regulations of an unlisted country in order for an unapproved drug to be exported to that country under section 802(b)(2). These components are: (1) a process for premarket review and approval of drugs; (2) good manufacturing practice controls; (3) requirements for adverse drug reaction reporting and the authority to remove drugs found to be unsafe or ineffective; and (4) requirements concerning drug advertising and promotion. FDA has determined that Argentina's laws governing the regulation of drugs contain these four components.

A. Section 802(b)(2)(B)(i)

First, for a drug to be exported under section 802(b)(2) of the FD&C Act, FDA must make a determination concerning the country's approval framework for drugs that involves several interrelated elements. These elements are:

- That there are statutory or regulatory requirements which require the review of drugs for safety and effectiveness;
- That this review must be conducted by an entity of the country's government;
- That the statutory or regulatory requirements authorize the approval of only those drugs that have been determined to be safe and effective;

- That there are statutory or regulatory requirements that the determination of safety and effectiveness be made by experts employed by or acting on behalf of such government entity and qualified by scientific training and experience to evaluate the safety and effectiveness of drugs;
- That there are statutory or regulatory requirements that the investigation be conducted by experts qualified by scientific training and experience to evaluate that safety and effectiveness of drugs.

1. Review of Drugs for Safety and Effectiveness by a Government Entity

According to Chapter II, Article 2 of Decree No. 150/1992, the "commercialization of proprietary medicines or pharmaceutical specialties"[5] in Argentina is "subject to the prior approval of the national health authority." Decree No. 150/1992, at Chapter II, Article 2 (April 12, 2019 submission). Proprietary medicines or pharmaceutical specialties (hereinafter referred to as "drugs")[6] that are approved for distribution in Argentina will be registered by the national health authority. *Id*. Decree No. 150/1992 indicates that, in general, Argentina prohibits the marketing or free delivery of drugs that are not registered with the health authority. *Id*. According to the marketing authorization included in Hemispherx's May 14, 2018 submission, ANMAT is the Argentinian government entity that is responsible for registering drugs that are approved for distribution. *See* ANMAT Marketing Authorization, Disposition #9358 (May 14, 2018 submission, Attachment 1).

Articles 3 through 5 in Chapter II of Decree No. 150/1992 identify the information that must be included in the application for registration of a drug. The required information varies depending on whether the drug has already been approved and is being marketed in another country. Article 5 applies to drugs for which there is no similar product already registered in Argentina and that are not marketed in any countries listed in Annex I[7] of the decree. Article 5 requires that the application to register a drug include information on the product (e.g., name, formula, dosage form, pharmacological classification, distribution condition); technical information (e.g., control method, shelf life period, manufacture method "in accordance with the

[5] Decree No. 150/1992 defines the term "medicinal products" to mean "[a]ny preparation or pharmaceutical product used to prevent, diagnose, and/or treat a disease or pathological condition, or to modify physiological systems for the benefit of the person to whom it is administered." The decree defines the term "proprietary medicines or pharmaceutical specialties" to mean "[a]ny medicinal product, designated by a conventional name, whether or not a manufacturing brand or trademark, or by the generic name corresponding to its composition and distribution, with a defined, declared and verifiable quantitative composition, a stable pharmaceutical form and a demonstrable therapeutic effect."

[6] As noted above in footnote 4, the phrase "proprietary medicines or pharmaceutical specialties" is defined in Chapter I, Article 1 of Decree No. 150/1992. For ease of discussion, our use of the term "drugs" throughout this document encompasses the Argentinian term of art "proprietary medicines or pharmaceutical specialties."

[7] The Annex I countries are the United States, Japan, Sweden, Swiss Confederation, Israel, Canada, Austria, Germany, France, United Kingdom, the Netherlands, Belgium, Denmark, Spain, and Italy.

appropriate manufacturing practices in force," bioavailability data); labeling information with clinical indications, warnings, precautions, drug interactions, adverse effects, dosage information, and form of administration; documentation demonstrating the product's safety and effectiveness for the proposed use; and a CGMP certificate from Argentina or an Annex I country. *See* Decree No. 150/1992, Chapter II, Articles 3, 5 (April 12, 2019 submission).

In addition, the translated marketing authorization for Ampligen® indicates that ANMAT reviewed the preclinical and clinical data that Hemispherx submitted for the drug. This translation states that, "having analyzed the background and evaluated the quality, efficacy and safety of the drug, [ANMAT] concludes that the risk-benefit ratio presented is acceptable, which supports its approval for sale for the proposed indication." ANMAT Marketing Authorization, Disposition #9358 (May 14, 2018 submission, Attachment 1).

Based on the translated documents submitted by Hemispherx, FDA determines that, in Argentina, there are statutory or regulatory requirements that require the review of drugs for safety and effectiveness and require that this review be conducted by an entity of the country's government. This determination is based on FDA's assessment of the translated documents that were submitted by Hemispherx and does not reflect an assessment of the implementation of these requirements by any entity of the Argentinian government.

2. Approval Only of Drugs Determined to Be Safe and Effective

As discussed above in Section III.A.1., Argentinian law requires the submission of information demonstrating that a drug is safe and effective for its proposed use in an application to register a drug. In addition, the translated marketing authorization for Ampligen® indicates that ANMAT reviewed the preclinical and clinical data that Hemispherx submitted for the drug. This translation states that, "having analyzed the background and evaluated the quality, efficacy and safety of the drug, [ANMAT] concludes that the risk-benefit ratio presented is acceptable, which supports its approval for sale for the proposed indication." ANMAT Marketing Authorization, Disposition #9358 (May 14, 2018 submission, Attachment 1).

Based on the translated documents submitted by Hemispherx, FDA determines that, in Argentina, there are statutory or regulatory requirements that authorize the approval of only those drugs that have been determined to be safe and effective. This determination is based on FDA's assessment of the translated laws and marketing authorization that were submitted by Hemispherx and does not reflect an assessment of the implementation of these regulatory requirements by any entity of the Argentinian government.

3. Determination by Qualified Experts

Like U.S. laws and regulations governing approval of drugs,[8] the translated Argentinian laws that FDA reviewed do not discuss whether decisions on applications for drug registrations must be made by qualified experts. The need for expert qualifications, however, is implicit in the nature of the scientific and medical decisions that are required to be made to register a drug in Argentina.

Based on the translated documents submitted by Hemispherx, FDA determines that, in Argentina, there are statutory or regulatory requirements that require that the determination of safety and effectiveness be made by experts employed by or acting on behalf of such entity and qualified by scientific training and experience to evaluate the safety and effectiveness of drugs. This determination is based on FDA's assessment of the translated documents that were submitted by Hemispherx and does not reflect an assessment of the implementation of these regulatory requirements by any entity of the Argentinian government.

4. Adequate and Well-Controlled Investigations Conducted by Qualified Experts

The translations made available to FDA do not use the term "adequate and well-controlled investigations, including clinical investigations," to describe the basis for a registration determination. However, Argentinian law and regulations require the submission of data from non-clinical and clinical tests in an application to register a drug. In addition, the Argentinian laws and regulations contain standards that address the quality and reliability of clinical investigations.

As discussed above, in Section III.A.1., Decree No. 150/1992 states that documentation proving a drug's safety and efficacy must be included in an application for registration. ANMAT also has issued regulations governing Good Clinical Practices (GCPs) for clinical trials. In ANMAT Disposition 6677/10, the "Regulatory Guideline for Good Clinical Practices in Clinical Pharmacology Studies," ANMAT explains that the Good Clinical Practices (GCPs) are "ethical and scientific standards which set out guidelines for the design, conduct, recording and reporting of studies" that involve human subjects. As scientifically validated clinical testing is needed to demonstrate the safety and efficacy of a new active pharmaceutical ingredient (API), ANMAT's GCP regulations apply to clinical trials that have "a registry and/or regulatory purpose" and seek to "provide an assurance of the quality and integrity of

[8] The U.S. statutory standards for approving drugs can be found at section 505 of the FD&C Act. 21 U.S.C. § 355. The regulations addressing approval of drugs can be found at 21 C.F.R. Part 314. None of these statutory or regulatory provisions speak to the qualifications of the FDA employees that make drug or biologic approval determinations.

the information produced" by clinical trials. ANMAT Disposition 6677/10, Section A.

Similar to provisions in 21 C.F.R. 314.126 (FDA's regulation on adequate and well-controlled clinical investigations), ANMAT's GCP regulations require that clinical studies be described in a clear and detailed protocol that, among other requirements, describes:

- the problem to be investigated and the study hypothesis
- the purpose of the research study design and justification
- criteria for including/excluding participants
- methods to reduce bias
- methods for reviewing study data to evaluate drug efficacy

These rules also require that clinical investigations be conducted by investigators who have appropriate qualifications and training, and that they be monitored by persons who have the proper scientific and/or clinical knowledge to perform that duty. *See* ANMAT Disposition 6677/10, Sections B, C.

Based on the translated documents submitted by Hemispherx, FDA determines that, in Argentina, there are statutory or regulatory requirements that the determination of safety and effectiveness be based on adequate and well-controlled investigations, including clinical investigations, conducted by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs. This determination is based on FDA's assessment of the translated laws and regulations submitted by Hemispherx and does not reflect an assessment of the implementation of these regulatory requirements by any entity of the Argentinian government.

B. Section 802(b)(2)(B)(ii)

Second, under section 802(b)(2)(B)(ii) of the FD&C Act, FDA must determine that Argentina possesses statutory or regulatory requirements that the methods used in, and the facilities and controls used for the manufacture, processing, and packing of drugs in the country are adequate to preserve their identity, quality, purity, and strength.

The ANMAT CGMP Standard establishes CGMP requirements for manufacturers, importers, and exporters of drugs for human use. These requirements address the methods used in and facilities used for the production, packaging, and holding of drugs, and are intended to ensure "that the production and control of pharmaceutical products are consistent with the quality standards adequate to their intended use and as per the Marketing Authorization … requirements and product specifications." ANMAT CGMP Standard, Chapter 1, Good Manufacturing Practices for pharmaceutical products, at section 1.8. In addition, drug manufacturers must be licensed by ANMAT and are subject

to regular inspection by the national health authority. *See id.*, at Chapter 1, Pharmaceutical Quality System, "Principle."

Based on the translated documents, FDA determines that, in Argentina, there are statutory or regulatory provisions that require that the methods used in, and the facilities and controls used for the manufacture, processing, and packing of drugs in the country be adequate to preserve their identity, quality, purity, and strength. This determination is based on FDA's assessment of the translated laws and regulations that were submitted by Hemispherx and Argentina and does not reflect an assessment of the implementation of these regulatory requirements by any entity of the Argentinian government.

C. Section 802(b)(2)(B)(iii)

Third, under section 802(b)(2)(B)(iii) of the FD&C Act, FDA must determine that there are statutory or regulatory requirements for the reporting of adverse reactions to drugs and procedures to withdraw approval and remove drugs found not to be safe or effective.

ANMAT Disposition 5358/2012 establishes requirements for Good Pharmacovigilance Practices. Compliance with the pharmacovigilance provisions is mandatory for drug registration and marketing authorization holders, and failure to comply "shall subject the offenders to the penalties provided for in the Drug Law No. 16463 and Decree No. 341/92." ANMAT Disposition 5358/2012, Articles 1, 4. The disposition states that the purpose of having marketing authorization holders comply with these provisions "is to guarantee the authenticity and quality of the safety data, for the continuous assessment of the risks associated to the proprietary medicines" that they sell. *Id*. at Annex I. Holders of a drug registration and marketing authorization must record and report "serious suspected adverse reactions occurring in Argentina" associated with both approved and off-label uses to ANMAT's Pharmacovigilance Department. Id. ANMAT also requires that marketing authorization holders periodically report "all national and international suspected adverse reactions." *Id*. There are specific forms that must be used to communicate adverse events to ANMAT. *See id*. at Annex II.

The pharmacovigilance provisions require that marketing authorization holders continuously evaluate their drugs' risk-benefit profile "and communicate immediately to the ANMAT all [the] new information that can have an impact on the overall assessment" of the drug's risks and benefits. *Id*. at Annex I. The pharmacovigilance provisions state that ANMAT will perform routine and targeted inspections to ensure that drug marketing authorization holders comply with these requirements. *See id*. In addition, the translated marketing authorization for Ampligen® states that Hemispherx "must comply with periodic safety reporting every six months for the first year of effective trade of the drug and, subsequently, each time the risk-benefit ratio is modified; thereby, ANMAT shall be

able to monitor closely the safety and efficacy achieved through the administration of the medicinal specialty in the indicated population throughout the drug's entire life cycle." ANMAT Marketing Authorization, Disposition #9358 (May 14, 2018 submission, Attachment 1).

Based on the translated documents submitted by Hemispherx, FDA determines that, in Argentina, there are statutory or regulatory requirements for the reporting of adverse reactions to drugs and procedures to withdraw approval and remove drugs found not to be safe or effective. This determination is based on FDA's review of the translated documents that were submitted by Hemispherx and does not reflect an assessment of the implementation of these regulatory requirements by any entity of the Argentinian government.

D. Section 802(b)(2)(B)(iv)

Fourth, under section 802(b)(2)(B)(iv) of the FD&C Act, FDA must determine that there are statutory or regulatory requirements that the labeling and promotion of drugs must be in accordance with the approval of the drug.

Decree No. 150/1992 requires that drug product labels bear particular information (e.g., manufacturer name and address, name of the product, generic drug name, pharmaceutical form, expiration date, storage information and sale condition, batch number and manufacturing series, the phrase "medicinal product approved by ANMAT, certificate no. XX"). The decree also requires that applications for marketing authorization and registration of a drug submit the product labeling and package inserts. The labeling must include the drug's pharmacological and therapeutic action(s), clinical indications, warnings, precautions, drug interactions and possible adverse effects, along with dosage information and form of administration. *See* Decree No. 150/1992 at Chapter II, Article 3.

The translated ANMAT marketing authorization for Ampligen® states that the agency determined the "indication referred to, as well as the dosage, route of administration, conditions of sale, and labeling and package inserts are considered to be acceptable, with the product studied meeting the requirements set forth under legal regulations in force." ANMAT Marketing Authorization, Disposition #9358 (May 14, 2018 submission, Attachment 1). The document also states "[t]he texts from the labeling and package insert(s) are hereby approved." *Id.*

Based on the translated documents submitted by Hemispherx, FDA determines that, in Argentina, there are statutory or regulatory requirements that the labeling and promotion of drugs must be in accordance with the approval of the drug. This determination is based on FDA's assessment of the translated documents submitted by Hemispherx and does

not reflect an assessment of the implementation of these regulatory requirements by any entity of the Argentinian government.

IV. Conclusion

Based on the translated documents provided in your submissions and for the reasons set forth above, FDA has determined that, in Argentina, there are statutory or regulatory requirements as specified in section 802(b)(2)(B) of the FD&C Act. If there are any changes to the Argentinian statutes or regulations, this determination may no longer apply. To ensure the export of Ampligen® continues to comply with all requirements in section 802(b)(2)(B), Hemispherx should notify FDA of changes in the marketing status of Ampligen® in Argentina and changes to Argentine law that could affect FDA's determination in this letter. Also, again, please be advised that this determination is based on FDA's assessment of the translated documents that were submitted by Hemispherx and does not reflect an assessment of the implementation of these regulatory requirements by any entity of the Argentinian government. Finally, please note that the appropriate Argentinian governmental entities are responsible for the application of Argentine laws to the importation and distribution of this product in Argentina; the FDA acknowledgement and determinations contained in this letter are not intended to supplant the application of Argentine law to Ampligen®.

Be advised that any exports under section 802 of the FD&C Act also must comply with the additional requirements of section 802(b)(2), described above in section II, as well as the requirements of section 802(f) and (g) of the Act, including the recordkeeping and notification requirements. FDA's implementing regulations for the notification and recordkeeping requirements can be found at 21 C.F.R. § 1.101.

Sincerely,

/S/

Ilisa B.G. Bernstein, Pharm.D., J.D.
Deputy Director
Office of Compliance
Center for Drug Evaluation and Research