J. Ben Haas
Latham & Watkins LLP
555 Eleventh Street, N.W., Suite 1000
Washington, DC 20004-1304

Re: Docket No. FDA-2019-P-6044

Dear Mr. Haas:

This letter responds to your citizen petition (Petition) submitted on behalf of Par Sterile Products, LLC (Par or Petitioner), that was received by the Food and Drug Administration (FDA, Agency, or we) on December 20, 2019. The Petition requests that:

(1) FDA expedite its review and take final action as soon as possible on Par's pending prior approval supplements (PASs) proposing to remove the epinephrine overage[1] from Adrenalin;

(2) FDA refrain from approving any abbreviated new drug application (ANDA) for an epinephrine injection product citing Par's Adrenalin as the reference listed drug (RLD) until FDA has completed its review of the pending PASs; and

(3) If FDA approves Par's pending PASs, FDA refrain from approving any ANDA for an epinephrine injection product that cites Par's Adrenalin as the RLD and that contains an epinephrine overage (or that otherwise fails to demonstrate that it is the "same as" the new Adrenalin formulation).[2]

We have carefully considered the Petition and all comments submitted to the docket. For the reasons described below, the Petition is denied. Also, today, FDA has approved International Medication Systems, Ltd.'s ANDA 211880 for Epinephrine Injection, USP, 30 milligram (mg)/30 milliliter (mL) (1 mg/mL, multiple dose vial), indicated: (1) for emergency treatment of allergic reactions (Type 1), including anaphylaxis; and (2) to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.[3]

[1] The term *overage* is applied in several different ways within the pharmaceutical drug design and manufacturing process. The Petition appears to use the term *overage* to refer to a *stability overage* or a *true overage*, which is an additional amount of active ingredient present in the finished product in excess of the labeled amount, added for the purpose of ensuring that the potency complies with specifications throughout the shelf life of the drug, to compensate for losses due to degradation of the active ingredient over time. For the purposes of this Petition response, we will use the terms *overage* and *stability overage* interchangeably.
[2] Petition at 2.
[3] A copy of the ANDA 211880 approval letter and approved labeling are available on FDA's web page at https://www.accessdata.fda.gov/scripts/cder/daf/.

I. FACTUAL AND LEGAL/REGULATORY BACKGROUND

A. Adrenalin

Par[4] is the sponsor of two new drug applications (NDAs) for Adrenalin (epinephrine injection) 1 mg/mL (NDAs 204200 and 204640).[5] FDA approved NDA 204200 for a 1 mL single dose vial of Adrenalin on December 7, 2012, and NDA 204640 for a 30 mL multiple dose vial of Adrenalin on December 18, 2013, for the following indications: (1) emergency treatment of allergic reactions (Type 1), including anaphylaxis; and (2) induction and maintenance of mydriasis during intraocular surgery.[6] The mydriasis indication was later removed in September 2016 (NDA 204200/S-004) based upon a change in formulation (as described below). An additional indication to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock was later approved on January 29, 2019 (NDA 204200/S-009, NDA 204640/S-009).[7] Both the Adrenalin 1 mL single dose and the 30 mL multiple dose vials contain the same active and inactive ingredients, with the exception of chlorobutanol used in the multiple dose vial presentation as a preservative.[8]

FDA approved Adrenalin with a stability overage of 14 percent (1.14 mg/mL) of the active pharmaceutical ingredient (API) epinephrine due to the observed instability of epinephrine and its degradation over time.[9] Epinephrine has two optical isomers: the naturally occurring endogenous form, L-epinephrine; and its isomer, D-epinephrine. L-epinephrine has approximately 10 to 15 times more systemic activity (when measured by systemic effects on blood pressure, etc.) than D-epinephrine.[10,11] The drug substance is manufactured as L-epinephrine. Aqueous formulations of L-epinephrine are chemically unstable as epinephrine is readily oxidized. L-epinephrine degrades over time and forms D-epinephrine, a degradant that increases over the epinephrine product shelf life. As higher levels of D-epinephrine and other

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[4] Par was previously known as JHP Pharmaceuticals, LLC.

[5] Any references to "Adrenalin" in this document are intended to cover both the 30 mL multiple dose vial and 1 mL single dose vial.

[6] This mydriasis indication was only approved for NDA 204200 since it would be inappropriate to use a multiple dose vial for different patients in an operating room. See original approved labeling for the 1 mL single vial dose of Adrenalin at https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204200s000lbl.pdf; and the updated approved labeling for Adrenalin at the time of approval of the 30 mL multiple dose vial at https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204640s000lbl.pdf.

[7] See last approved labeling for Adrenalin at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204200Orig1s009,204640Orig1s009lbl.pdf.

[8] Id. In the 1 mL vial, each 1 mL of Adrenalin solution contains: 1 mg epinephrine, 7.3 mg sodium chloride, 0.457 mg sodium metabisulfite, 1 mg sodium hydroxide, 2.25 mg tartaric acid, 0.20 mg disodium edetate dihydrate, hydrochloric acid to adjust pH, and water for injection. In the 30 mL vial, each 1 mL of Adrenalin solution contains 1 mg epinephrine, 6.15 mg sodium chloride, 0.457 mg sodium metabisulfite, 0.920 mg sodium hydroxide, 2.25 mg tartaric acid, 0.20 mg disodium edetate dihydrate, hydrochloric acid to adjust pH, 5.25 mg chlorobutanol as a preservative and water for injection.

[9] Petition at 5, footnote 19.

[10] Patil, PN, Miller, DD, and U Trendelenburg, 1975, Molecular Geometry and Adrenergic Drug Activity, Pharmacological Reviews 26(4):323-393.

[11] Westfall, TC and DP Westfall, 2011, Adrenergic Agonists and Antagonists, Brunton, LL, Chabner, BA, and BC Knollmann, eds., Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e, New York, McGraw-Hill: 257-295.

degradants (including epinephrine sulfonic acid) are formed over the shelf life of an epinephrine product, the potency gradually decreases. Adrenalin includes the excipient sodium bisulfite to decrease the rate of epinephrine oxidation.

FDA has approved applications for epinephrine products that currently specify some degree of stability overage to account for the decrease in potency over the shelf life due to the inherent instability of epinephrine. Although other epinephrine drug formulations are approved with some amount of overage of epinephrine, the Agency approved Adrenalin with a relatively large overage of 14 percent due to the instability of epinephrine and high levels of impurities in its original formulation.[12] Consequently, the 1 mL single dose Adrenalin product (NDA 204200) was approved with a postmarketing commitment (PMC 1977-1) to "evaluate formulation and process improvements to reduce the levels of impurities with Adrenalin (epinephrine injection)."[13] The approval letter for the 30 mL multiple dose Adrenalin product (NDA 204640) also contained a postmarketing commitment (PMC 2120-1) in which Par agreed to conduct a leachable study for the drug product.[14] The postmarketing commitments were intended to improve the quality and stability of the Adrenalin formulation(s). The overage was allowed to ensure that the delivered dose of epinephrine was within the labeled dose throughout the granted expiry dating period for the drug product(s). The overage in Adrenalin did not raise safety concerns regarding excessive dosing or exposure to the API. Adrenalin's overage was justified due to the known instability of epinephrine, which created a risk of a subpotent dose, and was within the acceptable range of 15 percent stated in the U.S. Pharmacopeia (USP) epinephrine injection monograph.[15]

To address PMC 1977-1, Par submitted supplements proposing formulation changes for a more stable Adrenalin product for the multiple dose vial (NDA 204640/S-002) on March 31, 2015, and for the single dose vial (NDA 204200/S-004) on January 8, 2016.[16] The stability overage of epinephrine in these new formulations remained unchanged at 14 percent.[17] Both supplements (NDA 204640/S-002 and NDA 204200/S-004) were approved on December 23, 2015, and September 12, 2016, respectively. The mydriasis indication was removed for the single dose vials (NDA 204200) as a consequence of this formulation change. The product expiry periods were extended to 24 months for both Adrenalin presentations, which constituted a significant improvement in comparison to expiry periods approved for previous formulations (i.e., 14 months for the multiple dose vial and 18 months for the single dose vial).[18]

On September 13, 2019, Par submitted a Changes Being Effected in 30 Days (CBE-30)

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[12] Petition at 1, 4-5.
[13] See Adrenalin NDA 204200 original approval letter at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/204200Orig1s000ltr.pdf.
[14] See Adrenalin NDA 204640 original approval letter at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/204640Orig1s000ltr.pdf.
[15] Petition at 5. See U.S. Pharmacopeia, *United States Pharmacopeia and National Formulary* (USP43-NF38 – 1648; USP42-NF37 – 1616; USP41-NF36 – 1530) (currently official on April 10, 2020).
[16] Id.
[17] Petition at 6.
[18] Petition at 5-6. See CMC Review of NDA 204640 (December 11, 2013) at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204640Orig1s000ChemR.pdf.

supplement to NDA 204640 notifying FDA that it was planning to market a new formulation of Adrenalin with no overage for its 30 mL presentation and shorten the drug product expiry from 24 months to 18 months. Par notes that this CBE-30 was in response to an out of specification result on a manufacturing lot that contained epinephrine above the upper limit of 115 percent.[19] Par claims to have considered reducing the specification for the overage from 114 percent to 113 percent and discovered that, in light of the 2015-2016 reformulation of Adrenalin, it may be possible to eliminate the overage.[20]

FDA informed Par that the proposed changes required approval pursuant to a PAS, and Par's CBE-30 was considered to be a PAS, NDA 204640/S-012.[21] On November 18, 2019, Par submitted an amendment to NDA 204640/S-012 to provide additional stability data.[22] On December 13, 2019, Par submitted a PAS, NDA 204200/S-011, for its 1 mL Adrenalin product to allow for a formulation that bears no overage.[23] As of today's date, NDA 204200/S-011 and NDA 204640/S-012 have not been approved. Due to limitations on disclosure of confidential commercial information and trade secret information, we do not further address the status of Par's PASs in this response. At present, the approved Adrenalin products are still approved with the 14 percent overage of epinephrine as noted in the Petition.[24] The Adrenalin product approved in NDA 204640 is the RLD for ANDA 211880, approved today.

B. Legal/Regulatory Background

1. ANDA Approval

The Drug Price Competition and Patent Term Restoration Act of 1984[25] (the Hatch-Waxman Amendments) amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to add, among other things, section 505(j) (21 U.S.C. 355(j)), which established an abbreviated approval pathway for generic drugs. To obtain approval, an ANDA applicant is not required to provide evidence to independently establish the safety and effectiveness of its proposed drug product. Instead, an ANDA relies on FDA's previous finding that the RLD is safe and effective.[26] To rely on this finding, an ANDA applicant must, among other things, provide sufficient information to show that its drug product is bioequivalent to the RLD.[27] An ANDA applicant generally must

[19] Petition at 6.
[20] Id.
[21] Petition at 2.
[22] Petition at 7.
[23] Petition at 2.
[24] Petition at 5.
[25] Public Law 98-417.
[26] An *RLD* is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" (§ 314.3(b)) (21 CFR 314.3(b)). RLDs are identified in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluation* (the Orange Book), available at http://www.accessdata.fda.gov/scripts/cder/ob/.
[27] See, e.g., section 505(j)(2)(A)(iv) of the FD&C Act (21 U.S.C. 355(j)(2)(A)(iv)) (requiring "information to show that the new drug is bioequivalent to the listed drug"); § 314.3(b) (defining reference listed drug); § 314.94(a)(7) (21 CFR 314.94(a)(7)) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the RLD); and § 314.127(a)(6)(i) (21 CFR 314.127(a)(6)(i)) (stating that FDA will refuse to

also demonstrate, among other things, that the proposed drug product has the same active ingredient(s), route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD.[28] The scientific premise underlying the Hatch-Waxman Amendments is that bioequivalent drug products with the same active ingredient(s), route of administration, dosage form, and strength are therapeutically equivalent and may be substituted for each other.[29]

FDA must approve an ANDA unless it finds that, among other things: (1) the ANDA applicant has not provided sufficient evidence of the foregoing; (2) 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; (3) the inactive ingredients of the proposed drug are unsafe for use under the conditions prescribed, recommended, or suggested in the proposed labeling; or (4) 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.[30]

2. Section 505(q) of the FD&C Act

Section 505(q) of FD&C Act was added by section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85, 121 Stat. 823) and was amended by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144, 126 Stat. 993). Section 505(q) of the FD&C Act, as originally added by FDAAA, applies to certain citizen petitions and petitions for stay of Agency action that request that FDA take any form of action relating to a pending application submitted under section 505(b)(2) or (j) of the FD&C Act and governs the way these petitions are treated. Among other things, section 505(q)(1)(F) of the FD&C Act governs the time frame for final Agency action on a petition subject to section 505(q). Under this provision, FDA must take final Agency action on such a petition no later than 150 days after the date on which the petition is submitted. The Petition is subject to the requirements of section 505(q) of the FD&C Act since Par requests actions in the Petition that could have delayed approval of a then-pending 505(j) application.[31]

II. DISCUSSION

A. Request for Expedited Review and Final Action on PASs

Par requests that FDA expedite its review and take final action as soon as possible on its pending PASs proposing to remove the epinephrine overage from Adrenalin given the alleged significant

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approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the ANDA).

[28] Section 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act; see also § 314.94(a).

[29] Therapeutic equivalents are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling (§ 314.3(b)).

[30] Section 505(j)(4) of the FD&C Act; see also § 314.105(d) and 314.127.

[31] See the guidance for industry *Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug and Cosmetic Act* (September 2019) (505(q) guidance) at 5-8.

safety risks associated with an epinephrine overage and alleged significant patient benefit that will derive from the proposed formulation change.[32] Pursuant to 21 CFR 314.70(b)(4), an applicant may ask FDA to expedite review of a supplement for "public health reasons[.]"[33] However, the Petition does not raise valid public health reasons warranting expediting review, nor have significant safety risks associated with an approved epinephrine overage been shown. Therefore, we do not agree that the review of Par's pending PASs, NDA 204640/S-012 and NDA 204200/S-011, should be expedited.

The safety of epinephrine for use in anaphylaxis is well known based on over 100 years of clinical experience. Common self-limiting[34] adverse reactions associated with epinephrine use include tremor, dizziness, palpitations, and headache. Serious adverse events include cardiotoxicity (i.e., myocardial ischemia and arrhythmias) and cerebral hemorrhages due to the rapid rise in blood pressure associated with epinephrine use.

Based upon published case reports, cardiac adverse events from epinephrine use are rare and generally occur with intravenous (IV) dosing, highlighting the need to proceed with caution if considering epinephrine by this route. These adverse events are usually secondary to overdosage or overly rapid rate of IV infusion at a rate inconsistent with current approved labeling, however, some patients have survived massive overdoses of epinephrine with no evidence of myocardial ischemia. Intramuscular (IM) and subcutaneous (SC) are the approved routes of administration for epinephrine for treatment of anaphylaxis. Epinephrine is labeled for IV administration for treatment of hypotension associated with septic shock. In this clinical scenario, patients are administered a titrated IV dosage form of epinephrine in a monitored hospital setting. The epinephrine overage in the currently approved formulation of Adrenalin does not significantly increase chances of an overdose when administered in accordance with the approved labeling.

In 2018, FDA's Office of Surveillance and Epidemiology (OSE) performed a pharmacovigilance review evaluating the FDA Adverse Event Reporting System (FAERS) database for cardiovascular and cerebrovascular adverse events associated with SC and IM administration of epinephrine in the management of anaphylaxis. OSE identified 33 serious FAERS cases reporting 1 or more cardiovascular or cerebrovascular adverse events from December 1987 through September 2018. Twenty-six of these cases occurred after one dose of epinephrine and 7 cases occurred after multiple doses of epinephrine. In 31 of these cases, patients received approved doses of epinephrine and in 2 cases patients received overdoses. Although adverse events in FAERS database may be underreported, the fact that there were so few cases of cardiovascular and cerebrovascular adverse events reported in over a 30-year time span is reassuring given the long-standing use of epinephrine along with the numerous epinephrine products on the market.

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[32] Petition at 1, 7-8. See also Exhibit 1 to the Petition.

[33] 21 CFR 314.70(b)(4) states that a supplement requesting expedited review should be plainly marked "Prior Approval Supplement-Expedited Review Requested." Neither of Par's PASs (one of which was originally submitted as a CBE-30) was marked as a request for expedited review at the time of submission.

[34] The term "self-limiting" refers to symptoms that resolve on their own without the need for medical treatment or intervention.

The pharmacokinetics and pharmacodynamics relationship for epinephrine with respect to safety is not well-established. As such, a critical dose of epinephrine that increases the safety risk is also not established. Moreover, the USP epinephrine injection monograph includes an upper assay limit of 15 percent,[35] and Adrenalin's current 14 percent epinephrine overage falls within this upper assay limit. Consistent with this, the known safety profile of epinephrine reflects products with overages similar to Adrenalin. If FDA had concerns that there were unacceptable safety risks with the epinephrine overage, we would not have approved the original formulation of the Adrenalin NDA and would have required that Par address the epinephrine overage prior to initial approval.

There have not been any postmarketing events in Par's periodic safety reports that have changed the known risk benefit profile of Adrenalin since its first approval in 2012. Furthermore, FDA's reviews of the narratives in FAERS provided since the reformulation approved in 2015 and 2016 under NDA 204640/S-002 and NDA 204200/S-004 did not identify any new adverse events associated with its recommended usage and dosages. Given the combination of few cases of cardiovascular and cerebrovascular adverse events reported in FAERS, the few literature reports of serious adverse events, and the lack of changes detected in the periodic safety reports since the reformulation, FDA has determined the safety risks of the existing epinephrine overage for Adrenalin are acceptable, and are comparable to the known safety profile for other approved epinephrine products.

Par claims that the proposed overage-free formulation will significantly reduce (if not eliminate) any potential for a super-potent dose of the active ingredient to be administered to patients.[36] Par also alleges that FDA's determination that the overage-free formulation requires prior FDA review and approval pursuant to a PAS "underscores the critical safety and effectiveness concerns implicated by this overage."[37] We disagree with both claims.

First, regarding the risk of super-potent doses, the approved epinephrine dose in adults and children (30 kilograms or more) for treatment of anaphylaxis is 0.3 mg to 0.5 mg, and the doses to increase mean arterial blood pressure in adults with hypotension associated with septic shock are titrated to achieve desired mean arterial pressure.[38] If epinephrine was dosed at full potency with overage (i.e., 1.14 mg/mL) for anaphylaxis, the administered doses would be 0.342 mg to 0.57 mg of epinephrine, respectively. These doses would not be super-potent. Second, regarding the need for the PAS, Adrenalin was approved with a 14 percent epinephrine overage to assure that an adequate dose of the API is available for emergency treatment despite the ongoing decrease in epinephrine content throughout the product's shelf-life (caused by the inherent instability of epinephrine in liquid formulations) and was determined to be safe for use with this overage. FDA is concerned that elimination of the epinephrine overage may put patients at risk of underdosing and not receiving enough epinephrine for life-saving, emergency-use treatment. Whether the improved stability of Adrenalin products reformulated in 2015 and

[35] See U.S. Pharmacopeia, *United States Pharmacopeia and National Formulary* (USP43-NF38 – 1648; USP42-NF37 – 1616; USP41-NF36 – 1530) (currently official on April 10, 2020).
[36] Petition at 6.
[37] Petition at 2.
[38] See last approved labeling for Adrenalin at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204200Orig1s009,204640Orig1s009lbl.pdf.

2016 supports an epinephrine overage less than 14 percent must be evaluated with adequate stability data to support that the labeled dose of epinephrine is available throughout the product shelf life.

Par has neither established any valid public health concern with Adrenalin or any other currently approved epinephrine products containing an overage, nor demonstrated that the proposed overage-free formulation of Adrenalin is safer or more effective than previously approved epinephrine products. There is no reason to justify FDA expediting review of NDA 204200/S-011 and NDA 204640/S-012 at this time.

B. ANDAs Citing Adrenalin as the Reference Listed Drug (RLD)

The Petition requests that FDA refrain from approving any ANDA for an epinephrine injection product citing Adrenalin as the RLD until our review of the pending PASs, NDA 204200/S-011 and NDA 204640/S-012, is complete.[39]

We deny this request. Section 505(j)(4) of the FD&C Act provides that the Agency "shall approve an [ANDA]" unless it finds that, among other things, (1) the ANDA applicant has not provided sufficient information required by section 505(j)(2)(A); (2) 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; (3) the inactive ingredients of the proposed drug are unsafe for use under the conditions prescribed, recommended, or suggested in the proposed labeling; or (4) 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.[40]

Consistent with the FD&C Act, the Agency declines the request to refrain from approving an ANDA, in connection with review of Par's PASs, if such an ANDA satisfies the relevant statutory and regulatory conditions for approval. Because we have concluded that International Medication Systems, Ltd.'s ANDA 211880 for Epinephrine Injection, USP, 30 mg/30mL (1mg/mL, multiple dose vial), referencing Par's currently approved Adrenalin product with a 14 percent overage as the RLD, meets all applicable statutory and regulatory requirements, we have, today, approved ANDA 211880.

The Petition also requests that, if FDA approves Par's pending PASs for the overage-free formulation, FDA refrain from approving any ANDA for an epinephrine injection product that cites Par's Adrenalin as the RLD and that contains an epinephrine overage (or that otherwise fails to demonstrate that it is the "same as" the new Adrenalin formulation).[41] It would be premature to respond to this request in the Petition at this time, including because we do not yet know if the PASs proposing the overage-free formulation of Adrenalin are approvable. If NDA 204200/S-011 and NDA 204640/S-012 are approved in the future, and Par believes this request from the Petition is still relevant, Par is welcome to submit a new citizen petition.

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[39] Petition at 2.

[40] See also § 314.105(d) ("FDA will approve an ANDA…if none of the reasons in § 314.127 for refusing to approve the ANDA applies.").

[41] Petition at 2.

III. CONCLUSION

For the reasons described above, the Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300121270, cn=Douglas C. Throckmorton -S
Date: 2020.04.24 12:25:23 -04'00'

Janet Woodcock, M.D.

Director
Center for Drug Evaluation and Research