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

CITIZEN PETITION

US WorldMeds, LLC (US WorldMeds) submits this petition under section 505(q) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) and 21 C.F.R. §§ 10.30 and 10.31 to request that the Commissioner of Food and Drugs (Commissioner) take the actions identified in Section A below.

We previously raised the issues discussed below in a citizen petition dated July 1, 2019.[1] The Food and Drug Administration (FDA or the Agency) denied that petition on November 27, 2019, on non-substantive grounds and "without comment" on our requests.[2] Shortly before

[1] *See* Docket No. FDA-2019-P-3192.

[2] Letter from Janet Woodcock, M.D., FDA, to Kristen L. Gullo, US WorldMeds, at 6 (Nov. 27, 2019). In guidance, FDA has explained its rationale for issuing this type of non-substantive denial:

> [W]e do not interpret section 505(q) [of the Federal Food, Drug, and Cosmetic Act] to require a substantive final Agency decision within 150 days on the approvability of a specific aspect of a pending application. In particular, we do not interpret section 505(q) to require such a decision when a final decision on the approvability of the application as a whole has not yet been made and when rendering such a decision could deprive an applicant of procedural rights established by statute and regulations. In such a situation, as described in the preceding sentence, we would expect in the ordinary course to deny a petition without comment on the substantive approval issue.

FDA, *Guidance for Industry*, *Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act*, at 15 (Rev. 2, Sept. 2019).

FDA issued its petition response, the Agency posted on Regulations.gov a comment that counsel for Sage Chemical, Inc. had submitted to the docket (Sage Comment).[3]

We submit the current petition to respond to the Sage Comment and ensure that FDA carefully considers these issues before approving any abbreviated new drug application (ANDA) that references APOKYN® (apomorphine hydrochloride injection). To facilitate FDA's review, we have kept this petition substantively the same as the prior petition with the addition of section III, which contains our response to the Sage Comment.

US WorldMeds is the holder of new drug application (NDA) 021264 for APOKYN. APOKYN is a non-ergoline dopamine agonist indicated for the acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced Parkinson's disease (PD).[4] APOKYN consists of a multi-dose glass cartridge (the APOKYN Cartridge) containing 10 mg/mL apomorphine hydrochloride solution for injection and a multiple-dose pen injector (the APOKYN Pen) to be used for administration of the drug product. Both the drug and device constituents of this combination product were approved in the APOKYN NDA.

We submit this petition to request that FDA require that any ANDA for a generic version of APOKYN seek approval of both the drug and device constituent parts of APOKYN.

US WorldMeds is filing this petition because FDA has not clarified whether the Agency will approve an ANDA for only the drug constituent part of a drug-device combination product that is approved in an NDA. For the reasons discussed below, as a legal matter, an ANDA cannot be approved for only the drug constituent part because the device constituent part is an integral part of the reference listed drug (RLD), and an ANDA applicant seeking approval of the drug constituent part only would be unable to satisfy the requirements to establish equivalency to the RLD product as a whole.

If FDA nonetheless concludes that an ANDA referencing a drug-device combination product is approvable for the drug constituent part alone—because, for example, it is compatible and can be administered with a separately approved or cleared general use injection device (*e.g.*, a general use needle injector for the administration of liquid medications)—such an approval pathway would not be available for generic versions of APOKYN given that no devices meeting this description appear to exist. US WorldMeds presently is not aware of any alternative auto-injectors or injector pens separately approved or cleared by FDA with technical specifications and/or intended uses consistent with the administration of apomorphine hydrochloride for its approved use. In accordance with its labeling, APOKYN can only be used "with a manual reusable, multiple-dose pen injector (APOKYN Pen)." Accordingly, an ANDA that does not

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[3] *See* Letter from Laurence S. Tauber, Cohen Tauber Spievack & Wagner P.C., to FDA re: Docket No. FDA-2019-P-3192 (Nov. 19, 2019) (Sage Comment). The certification states that the comment was submitted by "the attorney for Sage Chemical, Inc." *Id*. at 8.

[4] APOKYN Prescribing Information (May 2019) (including APOKYN® Pen Instructions for Use), https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021264s016lbl.pdf (attached as Ex. 1).

include its own device constituent part would be proposing the use of a generic drug constituent part with the APOKYN Pen.

That would be improper. FDA should not approve an ANDA for a drug constituent part to be used with the APOKYN Pen for three reasons.

First, the APOKYN Pen is approved only for use with the APOKYN Cartridge, so such an ANDA would invite an unapproved use of the APOKYN Pen.

Second, the ANDA applicant would be unable to comply with the combination product requirements that would apply because the labeling for a drug-only generic product would need to refer to the APOKYN Pen by name and/or description to provide appropriate dosage and administration instructions, effectively cross-labeling the generic drug constituent part to the RLD's device constituent part. The ANDA holder could not comply with the current good manufacturing practice (CGMP) requirements for combination products—in particular, design control requirements—because the device constituent part (*i.e.*, the APOKYN Pen) would be outside the control of the ANDA holder. Similarly, such an ANDA holder would be unable to comply with its postmarket safety reporting obligations with respect to the APOKYN Pen.

Third, an ANDA for the drug constituent part alone would raise practical concerns. Given the lack of control or coordination between the ANDA holder and device manufacturer, the ANDA holder would be unable to ensure that its product would remain compatible with any future versions of the APOKYN Pen. Moreover, it is uncertain that a patient who receives the generic cartridge would have, and would continue to have, an APOKYN Pen that could be used with the generic product.

These challenges have the potential to prevent the safe and effective use of the generic apomorphine hydrochloride product, which could exacerbate the motor symptoms of PD and reduce a patient's quality of life.

Finally, the lack of Agency guidance on whether it will approve an ANDA only for the drug constituent part of a drug-device combination product that is approved in an NDA—and, if so, under what circumstances—is an issue that extends to products beyond APOKYN. We therefore request, in addition, that FDA develop a policy framework setting forth the Agency's position on this issue in order to reduce uncertainty for innovators, generic drug developers, and other stakeholders.[5]

[5] In 2015, US WorldMeds submitted a citizen petition on a different issue related to APOKYN. In that petition, we requested that FDA require that ANDA applicants seeking approval of drug-device combination products containing apomorphine and intended for use in the advanced PD population address safety considerations through development and training programs designed to ensure that such devices meet the unique needs of this patient population. US WorldMeds, Citizen Petition, Docket No. FDA-2015-P-2626 (July 21, 2015). FDA denied that petition in 2017. FDA, Citizen Petition Response to US WorldMeds, Docket No. FDA-2015-P-2626 (Sept. 22, 2017).

A. Actions Requested

1. US WorldMeds respectfully requests that the Commissioner require that any ANDA referencing APOKYN seek approval of both the drug and device constituent parts of APOKYN.

2. US WorldMeds also requests that the Commissioner establish a policy framework clarifying the circumstances, if any, under which the drug constituent part of a generic drug-device combination product can be approved in an ANDA that does not also seek approval of the device constituent part.

B. Statement of Grounds

I. Background

A. Factual Background

1. Parkinson's Disease

Parkinson's disease is a progressive neurodegenerative disorder that affects multiple neurotransmitter systems (*e.g.*, serotonergic, noradrenergic, cholinergic systems) as well as nonmotor functions.[6] There currently is no cure for PD. Therefore, a primary goal of treatment is to help patients manage their symptoms, lower disease burden and improve their quality of life.[7]

The symptoms of PD are life-altering and include loss of motor control, referred to as an *off* state. *Off* states are the result of insufficient dopamine in the brain, and typically result in bradykinesia, resting tremor, rigidity, and postural instability.[8]

Bradykinesia is a severely disabling symptom and the most characteristic feature of an *off* state. It typically results in difficulties with planning, initiating and executing movements, and performing sequential and simultaneous tasks. Rigidity causes muscles that usually stretch when they move and relax when they are at rest to remain stiff and unable to rest. Rigidity frequently is associated with pain and can result in scoliosis and other postural deformities that

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[6] Aarsland D et al., *Cognitive Decline in Parkinson Disease*, NAT REV NEUROL. 2017 Apr;13(4):217–231. (attached as Ex. 2).

[7] National Institute of Neurological Disorders and Stroke (NINDS), *Parkinson's Disease: Hope Through Research* (last modified May 5, 2019), https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research/Parkinsons-Disease-Hope-Through-Research#Treatment (attached as Ex. 3).

[8] Obeso JA et al., *Past, Present, and Future of Parkinson's Disease: A Special Essay on the 200th Anniversary of the Shaking Palsy*, MOV DISOR. 2017 Sep;32(9):1264–1310 (attached as Ex. 4).

increase the risk of falls and hip fractures. The frequency of falls is related to the severity of the disease and the time spent *off*. [9]

Motor fluctuations are the cycling between *on* and *off* states. Clinical features of PD usually increase in severity with disease progression, and many patients develop worsening motor fluctuations despite treatment. *Off* episodes, which can occur when treatment has not taken effect or has worn off, can severely limit a patient's ability to perform daily tasks.[10] Increasingly unstable motor states fluctuating unpredictably between *off* and *on* episodes ultimately lead to loss of independence. Patients with advanced PD often require a caregiver or medical supervision. Patients may experience limitations in performing at work, and often avoid activities due to the fear of experiencing an *off* episode, which can result in social isolation.[11]

In later stages of PD, motor fluctuations are commonly accompanied by nonmotor symptoms (NMS) that result in cognitive impairment and/or dysautonomia, including dementia. Additional life-altering NMS include, among others, sleep and emotional problems, depression, difficulties in coordination and speech, and problems with balance and pain.[12]

In sum, the symptoms experienced during *off* episodes can have a significant adverse impact on a patient's quality of life,[13] making it important to timely and effectively manage these symptoms.[14]

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[9] Janovic J, *Parkinson's Disease and Movement Disorders: Moving Forward*, LANCET NEUROL. 2008 Jan;7(1):9–11 (attached as Ex. 5).

[10] *See* Pfeiffer RF et al., *Continued Efficacy and Safety of Subcutaneous Apomorphine in Patients with Advanced Parkinson's Disease*, PARKINSONISM RELAT DISORD. 2007 Mar;13(2):93–100 (attached as Ex. 6); US WorldMeds LLC, Off *Episodes*, https://www.apokyn.com/patients/off-Episodes (last accessed June 26, 2019) (attached as Ex. 7).

[11] *See* FDA, *The Voice of the Patient: Parkinson's Disease*, at 4–5 (Apr. 2016), *available at* https://www.fda.gov/media/97680/download (attached as Ex. 8); Parkinson's Found., *Managing PD Mid-Stride*, at 29–30, *available at* https://www.parkinson.org/sites/default/files/attachments/MidStride.pdf (attached as Ex. 9).

[12] *See* Schapira AHV, Chaudhuri KR, Jenner P, *Non-Motor Features of Parkinson Disease*, NAT REV NEUROSCI. 2017 Jul;18(7):435–450 (attached as Ex. 10).

[13] *See, e.g.*, Chiong-Rivero H et al., *Patients' and Caregivers Experiences of the Impact of Parkinson's Disease on Health Status*, PATIENT RELAT OUTCOME MEAS. 2011 Mar;2011(2):57–70 (attached as Ex. 11).

[14] *See* Chapuis S et al., *Impact of the Complications of Parkinson's Disease on the Quality of Life*, 20 MOV DISORD. 2005 Feb;20(2):224–30, 229 (concluding that because of the impact of motor complications on patient quality of life, it is important "to try to prevent the appearance of motor complications and, when they are present, to attempt to control them") (attached as Ex. 12); Stocchi F et al., *Early DEtection of wEaring off in Parkinson disease: The DEEP study*, PARKINSONISM RELAT DISORD. 2014 Feb;20(2):204–11, 209 ("Since [an *off* episode] can be effectively treated by changes in medication dose and kind its recognition is critical given [an *off* episode's] negative implications on quality of life.") (attached as Ex. 13); Schapira AHV, Chaudhuri KR, Jenner P, *supra* note 12, at 446 (stating that "non-motor problems are a significant, if not even the predominant, determinant of PD patients' quality of life").

2. APOKYN and the APOKYN Pen

APOKYN® (apomorphine hydrochloride injection), NDA 021264, is the only approved drug-device combination product containing apomorphine hydrochloride for use in the advanced PD population. FDA approved APOKYN on April 20, 2004 for the acute, intermittent treatment of hypomobility, "*off*" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced PD.[15]

APOKYN is a potent non-ergoline dopamine agonist.[16] APOKYN is believed to work by mimicking the activity of dopamine in the brain. Dopamine sends signals throughout the brain and, among other things, plays an important role in the control of locomotion.[17]

APOKYN has been shown to be effective in the treatment of *off* episodes associated with PD.[18] Because APOKYN is quickly absorbed, it can provide rapid relief for the symptoms that occur during *off* episodes when it is administered in a timely manner.[19] To safely and effectively manage *off* episodes, it is important to mitigate the risks of medication errors, including overdose, underdose, or missed doses. As further described below, the proper use of APOKYN—which necessarily includes the proper design and use of the APOKYN Pen—is imperative to achieve this goal. FDA repeatedly has expressed the importance of appropriate device design and its relationship to proper use, considerations that are addressed from a regulatory perspective through design controls.[20]

APOKYN is supplied in prefilled, multi-dose glass cartridges (30 mg/3 mL (10 mg/mL)) that are indicated for use only with a multiple-dose APOKYN Pen.[21] Similarly, the APOKYN Pen Instructions for Use (APOKYN Pen IFU) state that the APOKYN Pen is "[d]esigned to be used only with 3 mL APOKYN® (apomorphine hydrochloride injection) Cartridges."[22] The APOKYN Pen IFU are "patient labeling"[23] and, accordingly, are included with the product labeling and

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[15] APOKYN Prescribing Information § 1.

[16] *Id*. § 12.1.

[17] *See* US WorldMeds, *About APOKYN*, https://www.apokyn.com/patients/about-apokyn (last accessed June 26, 2019) (attached as Ex. 14).

[18] *See* Pfeiffer RF et al., *supra* note 10; US WorldMeds LLC, Off *Episodes*, *supra* note 10.

[19] Pfeiffer et al., *supra* note 10, at 94; APOKYN Prescribing Information § 12.3.

[20] As discussed further below, combination products that include a device constituent part must comply with the Quality Systems Regulation, which includes design controls. *See* 21 C.F.R. §§ 4.3(b), 820.30. *See also infra* nn. 36–39 and accompanying text (discussing CRL related to design issues).

[21] APOKYN Prescribing Information § 3.

[22] US WorldMeds, APOKYN® Pen Instructions for Use, at 1 (May 2019), https://www.apokyn.com/sites/all/themes/apokyn/content/resources/Apokyn_PPI.pdf#page=28 (attached as Ex. 15).

[23] *See* FDA, *Guidance for Industry, Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products—Content and Format*, at 3 (Dec. 2014) ("Under § 201.57(c)(18), if a product has FDA-approved patient labeling (e.g., Patient Package Insert, Medication Guide, and Instructions for Use), such labeling must be referenced in the PATIENT COUNSELING

referenced in the *Patient Counseling Information* section.[24] As further discussed below, the labeling indicates that the APOKYN Cartridges are to be used only with the APOKYN Pen and that the APOKYN Pen is to be used only with the APOKYN Cartridges.[25]

APOKYN typically is dispensed by specialty pharmacies.[26] The APOKYN Cartridges and the APOKYN Pen are distributed and packaged separately, and the APOKYN Pen is provided only to patients with a prescription for APOKYN (and at no additional cost). The APOKYN Cartridges are replaceable,[27] and patients with an APOKYN prescription can request replacement APOKYN Pens if, for example, they break or lose their Pens.[28]

APOKYN's labeling, including the APOKYN Pen IFU, is essential to the safe and effective use of APOKYN. APOKYN's labeling highlights the importance of using the APOKYN Cartridges only with the APOKYN Pen. For example, the labeling states that patients should be instructed "to follow the directions provided in the Patients Instructions for Use."[29] The APOKYN Pen IFU, in turn, instruct patients that the APOKYN Pen is for use only with 3 mL APOKYN Cartridges. They also state that the APOKYN Pen should not be used unless the patient and his or her caregiver have been taught the correct way to use the APOKYN Pen and unless both understand all of the instructions.[30] The labeling also illustrates the importance of understanding how to properly use the APOKYN Pen to administer the correct amount of the drug. For example, the APOKYN Pen IFU state (1) "**[d]o not** dial the dose or try to correct a dialing error with the pen needle in the skin. You could receive the wrong dose";[31] and (2) "[i]f you dial backwards, APOKYN will be pushed through the needle and you will lose medicine."[32]

INFORMATION section. The reference to patient labeling informs health care providers of the existence of approved patient labeling and should direct them to advise patients to read such labeling.").

[24] *See* APOKYN Prescribing Information § 17; 21 C.F.R. § 201.57(c)(18) (providing that section 17 of the PI, *Patient Counseling Information*, must, among other things, refer to any "FDA-approved patient labeling," and "the full text of such patient labeling must be reprinted immediately following this section or, alternatively, accompany the prescription drug labeling").

[25] *See* APOKYN Prescribing Information §§ 2.1, 3, 17; APOKYN Pen Instructions for Use at 1, 4.

[26] *See* US WorldMeds, *Starting APOKYN: Your APOKYN Delivery*, https://www.apokyn.com/patients/starting-APOKYN (last accessed June 26 2019) (attached as Ex. 16).

[27] *See* APOKYN Pen Instructions for Use, at 11 (directing patients to call their specialty pharmacy for replacement cartridges).

[28] *See, e.g.*, APOKYN Pen Instructions for Use, at 26–27 (directing patients to replace their APOKYN Pen by calling their specialty pharmacy provider or 1-877-7APOKYN if the pen does not work, if the dose numbers and/or white markers wear off, or if unable to read the dose numbers through the dose window)

[29] APOKYN Prescribing Information § 2.1.

[30] APOKYN Pen Instructions for Use, at 4.

[31] *Id*. at 7 (emphasis in original).

[32] *Id*. at 17.

3. The Role of Device Design in Ensuring Safe and Effective Use

FDA has made clear that the design of a device is critical to ensuring that it is used safely and effectively by patients and/or caregivers, stating that the Agency "is primarily concerned that devices are safe and effective for the intended users, uses, and use environments."[33] FDA seeks "to ensure that the device user interface has been designed such that use errors that occur during use of the device that could cause harm or degrade medical treatment are either eliminated or reduced to the extent possible."[34] Moreover, in guidance specific to ANDAs for drug-device combination products, FDA states that the Agency may request "additional information and/or data . . . to address whether [any design] differences identified in the user interface introduce a risk that might impact the clinical effect or safety profile of the generic combination product as compared to the RLD when the generic combination product is substituted for the RLD."[35]

In our discussions with the Agency, FDA has emphasized the importance of device design in preventing the potential safety and efficacy consequences associated with an underdose, dose omission, or overdose for PD patients. Specifically for APOKYN, the Agency has acknowledged that an underdose or dose omission could lengthen *off* episodes and increase risk of falls, and an overdose could lead to severe dyskinesia, orthostatic hypotension and syncope. Similarly, FDA highlighted its concern regarding the proper design and use of a drug-delivery device for DUOPA® (carbidopa and levodopa), which is indicated for the treatment of motor fluctuations in patients with advanced PD. DUOPA is administered into the jejunum through a percutaneous endoscopic gastrostomy with jejunal tube with the CADD®-Legacy 1400 portable infusion pump.[36] FDA issued a complete response letter (CRL) for DUOPA on March 28, 2014, requesting that DUOPA's sponsor, AbbVie, Inc., address a number of product design issues to minimize task failures and ensure administration of the appropriate dose.[37] FDA also expressed concerns about "operational difficulties," such as missed doses, that could "lead to suboptimal therapy, dyskinesia, loss of mobility, pain, and discomfort."[38] FDA approved DUOPA after additional information was provided that "acceptably addresse[d] the manufacturing, device performance, and human factors deficiencies that formed the basis of" the CRL.[39]

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[33] FDA, *Guidance for Industry and Food and Drug Administration Staff, Applying Human Factors and Usability Engineering to Medical Devices*, at 1–2 (Feb. 3, 2016).

[34] *Id.* at 2.

[35] FDA, *Draft Guidance for Industry, Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*, at 8 (Jan. 2017) [hereinafter *Comparative Analyses Draft Guidance*].

[36] DUOPA Prescribing Information §§ 1, 2 (Sept. 2016) (attached as Ex. 17).

[37] Complete Response Letter from Billy Dunn, FDA, to Matthew Kuntz, AbbVie Inc., at 12 (Mar. 28, 2014) (attached as Ex. 18).

[38] *Id.* at 7.

[39] FDA, Summary Review for Regulatory Action, NDA No. 203952, at 4 (Jan. 9, 2015) (attached as Ex. 19).

B. Statutory and Regulatory Background

1. New Drug Applications and Abbreviated New Drug Applications

Section 505 of the FDCA establishes the approval requirements for new drugs. To be approved, an NDA submitted under section 505(b) of the Act must, among other things, be supported by investigations showing that the drug is safe and effective for use. A section 505(b)(1) application is supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference or use.

The Drug Price Competition and Patent Term Restoration Act of 1984, frequently referred to as the Hatch-Waxman Amendments,[40] established the process for generic drug approval pursuant to an ANDA. Unlike an NDA, an ANDA is not required to provide evidence that independently establishes the safety and effectiveness of the proposed drug. Rather, an ANDA relies on FDA's prior finding that the RLD is safe and effective. An RLD is "the listed [*i.e.*, previously approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA."[41] Among other things, an ANDA generally must show that it has the same active ingredient(s), route of administration, dosage form, strength, and (with certain exceptions) labeling as the RLD.[42] An ANDA also must include sufficient information to demonstrate that the proposed drug is bioequivalent[43] to the RLD and that the ANDA meets the approval requirements relating to chemistry, manufacturing, and controls (CMC).[44]

2. Combination Products

APOKYN is a combination product. A "combination product" includes, among other things,

> [a] drug, device, or biological product packaged separately that according to its . . . proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be

[40] Pub. L. No. 98-417, 98 Stat. 1585 (1984).

[41] 21 C.F.R. § 314.3(b).

[42] *See, e.g.*, FDCA §§ 505(j)(2)(A), 505(j)(4); 21 C.F.R. §§ 314.94, 314.127.

[43] Bioequivalence is defined as:

> [T]he absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study . . . .

21 C.F.R. § 314.3.

[44] *See* FDCA § 505(j)(2)(A).

> changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose.[45]

APOKYN is comprised of two separately packaged products, a drug constituent part (apomorphine hydrochloride) and a device constituent part (the APOKYN Pen injector).[46] APOKYN meets the definition of "combination product" because each constituent part is intended for use only with the other constituent part; both constituent parts are required for the intended use, indication, or effect; and the labeling reflects that the constituent parts are intended only for use with each other.[47]

Section 503(g)(1) of the FDCA grants the Secretary of the Department of Health and Human Services[48] the authority to "assign a primary agency center to regulate products that constitute a combination of a drug, device, or biological product."[49] If the "primary mode of action"[50] of a combination product is determined to be that of a drug (other than a biological product), then the Center for Drug Evaluation and Research (CDER) "shall have primary jurisdiction."[51]

3. ANDAs for Drug-Device Combination Products

The ANDA approval requirements described above apply to all products submitted in ANDAs, including drug-device combination products.[52] As a general matter, when assessing the therapeutic equivalence of a proposed generic drug-device combination product, the Agency "will consider whether the generic product can be substituted with the expectation that it will have the same clinical effect and safety profile as the RLD when administered to patients under

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[45] 21 C.F.R. § 3.2(e)(3).

[46] The APOKYN labeling describes "[m]ulti-dose glass cartridges, 30 mg/3 mL (10 mg/mL) for use with a multiple-dose pen injector (APOKYN Pen)." APOKYN Prescribing Information, Highlights of Prescribing Information. In addition, the labeling states that "APOKYN is indicated for subcutaneous administration only . . . and only by a multiple-dose APOKYN Pen with supplied cartridges." *Id.* § 2.1.

[47] *See* FDA, *Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products*, at 3 (June 2013) [hereinafter *Technical Considerations for Pen, Jet, and Related Injectors Guidance*] ("When injectors are combined with, packaged with, or labeled for use with a specific drug/biological product they may be combination products.").

[48] The Secretary has delegated this authority to the Commissioner. *See* FDA, Staff Manual Guide § 1410.10, at 1 (Aug. 26, 2016).

[49] FDCA § 503(g)(1)(A).

[50] The "primary mode of action" is defined as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product." 21 C.F.R. § 3.2(m).

[51] FDCA § 503(g)(1)(D)(i).

[52] *See* section I.B.1, *supra*.

the conditions specified in the labeling."[53] The comparison between the generic combination product and the RLD includes consideration of the physical features of the RLD compared to the delivery device for use with the generic combination product. Indeed, FDA guidance states that "FDA recommends that the potential applicant of the proposed generic combination product acquire the RLD to examine (e.g., visual and tactile examination) the physical features of the RLD and compare them to those of the delivery device constituent part for the proposed generic combination product."[54] FDA also has stated that "ANDAs for a drug-led combination product [(*e.g.*, generic versions of APOKYN)] should also include sufficient information to demonstrate that the non-lead constituent part [(*e.g.*, a generic version of the APOKYN Pen)] is compatible for use with the final formulation of the drug constituent part."[55]

FDA has explained that a proposed generic combination product and its RLD do not necessarily have to be identical in all respects and that, for generic drug-device combination products, "differences in the design of the user interface[56] for a generic combination product as compared to the RLD may exist without precluding approval of the generic combination product under an ANDA."[57] However, the differences "should be adequately analyzed, scientifically justified, and otherwise not preclude approval under an ANDA."[58] FDA analyzes such differences on a case-by-case basis.[59]

When the device constituent part is included as part of the RLD and was approved under the NDA, an ANDA must include a corresponding device constituent part in the ANDA submission, and the required showing of sameness must take account of the device constituent part. FDA has stated that when reviewing a drug-delivery device combination product, the Agency "must evaluate the [device] constituent part of the combination product for which ANDA approval is sought to ensure that its performance characteristics and critical design attributes will result in a product that will perform the same as the RLD."[60] FDA has stated that it will refuse to receive an ANDA for a drug-device combination product if the device used to deliver the drug is not sufficiently similar to the device used to deliver the drug constituent part of the RLD.[61] If there are differences, human factors studies may be used to confirm that any

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[53] FDA, *Draft Guidance for Industry and FDA Staff, Principles of Premarket Pathways for Combination Products*, at 12 (Feb. 2019) [hereinafter *Premarket Pathways for Combination Products Draft Guidance*]; *see also* 21 C.F.R. § 314.3(b) (defining "reference listed drug").

[54] *Comparative Analyses Draft Guidance*, at 7.

[55] *Premarket Pathways for Combination Products Draft Guidance*, at 12.

[56] "The term user interface refers to all components of the combination product with which a user interacts." *Comparative Analyses Draft Guidance*, at 1.

[57] *Id.* at 2–3.

[58] *Premarket Pathways Draft Guidance*, at 12.

[59] *Id.*

[60] *See* FDA, Citizen Petition Response to King Pharmaceuticals, Inc., Docket Nos. FDA-2007-P-0128 & FDA-2009-P-0040, at 6 (July 29, 2009) [hereinafter King Petition Response].

[61] *See* FDA, *Guidance for Industry, ANDA Submissions – Refuse-to-Receive Standards*, at 17 (Dec. 2016, Rev. 2).

differences "are acceptable and that the proposed generic combination product can be substituted with the full expectation that the generic combination product will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling."[62]

Additionally, the CMC section of an ANDA submission for a drug-device combination product must include a general description of the entire delivery device constituent part. This includes "complete CMC information for the product, including the design of the delivery device constituent part and development information."[63] The application also must show that the delivery device constituent part is "compatible for use with the final formulation of the drug constituent part through appropriate studies."[64] These studies may include extractable/leachable studies, performance testing, and stability studies.[65] Comparative *in vitro* performance testing data also may "be needed to support the delivery device constituent part of the proposed generic combination product."[66] FDA also has stated that "[f]or prefilled injectors, co-packaged injectors, or injectors and drug/biologic distributed separately and marketed under [an] NDA/BLA, each premarket submission is reviewed and approved for a specific injector with a specific drug/biological product. . . . Therefore, the submission should include injector-drug/biological product specific data."[67]

4. CGMP and Postmarket Safety Reporting Requirements for Combination Products

Combination products must be manufactured in accordance with CGMP requirements as identified in 21 C.F.R. part 4.[68] This regulation requires a drug-device combination product to comply with the CGMP requirements for drugs[69] and the quality system (QS) requirements for devices, which are set forth in 21 C.F.R part 820.[70] The CGMP requirements in 21 C.F.R. part 820 include, among others, management responsibility,[71] design controls,[72] purchasing

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[62] *Comparative Analyses Draft Guidance*, at 3.

[63] *Id.*

[64] *Id.*

[65] *Id.*

[66] *Id.*

[67] *Technical Considerations for Pen, Jet, and Related Injectors Guidance*, at 10–11 (June 2013).

[68] *See* 21 C.F.R. part 4; *see also* 78 Fed. Reg. 4307 (Jan. 22 2013) (Current Good Manufacturing Practice Requirements for Combination Products Final Rule) (codified at 21 C.F.R. part 4).

[69] *See* 21 C.F.R. parts 210 and 211; *see also* 21 C.F.R. § 4.3(a).

[70] *Id.* part 820; *see also id.* § 4.3(b).

[71] *Id.* § 820.20.

[72] *Id.* § 820.30.

controls,[73] corrective and preventive action,[74] installation,[75] and servicing.[76] Combination products approved under ANDAs are subject to these same requirements.[77]

The design controls requirements are intended to "confirm that there are no negative interactions between constituent parts, and ensure that their combined use results in a combination product that is safe and effective and performs as expected."[78] For cross-labeled combination products, "the design control process and design history file for the device constituent parts of cross-labeled combination products should address the suitability of the device for use as part of the combination product, including the interactions and interrelationships between it and other constituent parts of the combination product."[79]

In addition, the holder of the marketing authorization for a combination product is responsible for complying with all aspects of the CGMP requirements applicable to the entire manufacturing process for the combination product and across all facilities.[80] This is true "even if the [holder] is not directly engaged in its manufacture."[81] When the holder is not directly engaged in the manufacture of one or all constituent parts of a combination product, FDA has stated that "quality agreements and audits can be helpful in assuring compliance with applicable CGMP requirements."[82] Such agreements "may, for instance, specify expectations as to which facility will perform what activities and develop and maintain what documentation needed to demonstrate compliance with particular CGMP requirements," and "what measures a facility will take to ensure compliance with CGMP requirements and any other relevant duties established by the owner for that facility."[83] FDA has recommended that "[e]ach manufacturing facility for a combination product should have documentation specifying its respective

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[73] *Id*. § 820.50.

[74] *Id*. § 820.100.

[75] *Id*. § 820.170.

[76] *Id*. § 820.200.

[77] *See* FDA, *Guidance for Industry and FDA Staff, Current Good Manufacturing Practice Requirements for Combination Products*, at 8–9 (Jan. 2017) [hereinafter *Combination Products CGMP Guidance*] ("For NDAs, BLAs, and ANDAs, the CGMP approach should be described in the Common Technical Document."); *id*. at 5 ("The final rule on CGMP requirements for combination products applies to all combination products."); *see also* 81 Fed. Reg. 92603 (Dec. 20, 2016) (Postmarketing Safety Reporting for Combination Products Final Rule); FDA, *Guidance for Industry and FDA Staff, Postmarketing Safety Reporting for Combination Products* (July 2019) [hereinafter *PMSR Guidance*].

[78] *Combination Products CGMP Guidance*, at 21.

[79] *Id*. at 22 n. 48.

[80] 78 Fed. Reg. at 4311; *see also Combination Products CGMP Guidance*.

[81] *Combination Products CGMP Guidance*, at 17.

[82] *Id*.

[83] *Id*. at 18.

responsibilities, and the manufacturer of the finished combination product [(*e.g.*, the holder of the marketing authorization)] should have access to this documentation."[84]

In addition, combination products are subject to postmarket safety reporting requirements.[85] Postmarket safety reports (PMSRs) must be submitted based on the application type (*e.g.*, NDA/ANDA or 510(k)) and the nature of the constituent part(s).[86] For example, for a drug-device combination product approved under an NDA or ANDA, the combination product applicant must comply with the PMSR requirements of 21 C.F.R part 314 *(i.e.*, NDA or ANDA-based reports) and must also comply with the following device-based reporting requirements: (1) 5-day reports under 21 C.F.R. §§ 803.53 and 803.56, (2) malfunction reports under 21 C.F.R. §§ 803.50 and 803.56, and (3) reports of corrections and removals under 21 C.F.R. part 806.[87]

II. Discussion

A. ANDAs referencing APOKYN should be required to seek approval of both the drug and device constituent parts.

1. An ANDA must include a device constituent part because the reference listed drug includes both drug and device constituent parts.

FDA has recognized that where a drug-delivery device combination product is the subject of an approved NDA, both the drug and device constituent parts comprise the RLD for an ANDA referencing that product.[88] This approach is consistent with the Agency's position that when reviewing a drug-delivery device combination product, FDA "must evaluate the [device] constituent part of the combination product for which ANDA approval is sought to ensure that its performance characteristics and critical design attributes will result in a product that will perform the same as the RLD."[89] Because the device is a constituent part of the RLD, a generic product referencing the drug-delivery device combination must include a proposed device constituent part and meet the ANDA approval requirements with respect to the entire RLD.

Here, APOKYN's delivery system (*i.e.*, the APOKYN Pen) is an integral part of the RLD. The APOKYN Pen is not separately approved or cleared and is not available except through a prescription for APOKYN. An ANDA that does not seek approval of a corresponding delivery device would omit a device constituent part that is an integral part of the RLD and, therefore, is

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[84] *Id*.

[85] *See* 21 C.F.R. part 4, subpart B.

[86] *See id.* § 4.102.

[87] *Id*. § 4.102(c)(1).

[88] *See*, *e.g.*, *Comparative Analyses Draft Guidance*, at 1 (recommending an analysis of "the proposed user interface for the generic drug-device combination product . . . compared to the user interface for the reference listed drug (RLD)"), 3 ("FDA intends to consider whether the generic combination product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to the use of the generic combination product."), & 6 (recommending a labeling comparison of the "descriptions of the delivery device constituent parts of the generic combination product and its RLD").

[89] King Petition Response, at 6.

necessary for FDA to determine whether the proposed generic product is equivalent to the RLD in terms of safety and effectiveness.[90] It follows, therefore, that an ANDA that references APOKYN as the RLD cannot be approved under section 505(j) of the FDCA unless the ANDA includes a delivery system for the generic drug.

2. Even if an ANDA could be approved for the drug constituent part alone for use with a device other than the APOKYN Pen, no such device is available here.

To our knowledge, FDA has not issued a clear public statement on whether the Agency would approve an ANDA for only the drug constituent part of a drug-device combination product approved in an NDA. FDA's thinking on this issue therefore remains unclear. It is possible, for example, that FDA might determine that an ANDA referencing a drug-device combination product is approvable for the drug constituent part alone based on data supporting the use of the generic drug constituent part with a device other than the RLD; for example, a general use device.

However, an ANDA referencing APOKYN would not fit this description. Although there are general use injectors that can be used with a wide range of legally marketed drugs,[91] we are not aware of any alternative auto-injectors or injector pens separately approved or cleared by FDA with technical specifications and/or intended uses consistent with the administration of apomorphine hydrochloride for its approved use. An ANDA referencing APOKYN therefore would need to include its own device constituent part. The alternative—using a generic drug constituent part with the APOKYN Pen—would be improper for the reasons set forth below.

3. An ANDA for a generic drug product to be used with the APOKYN Pen would require an unapproved use of the APOKYN Pen.

The use of a drug product other than the APOKYN Cartridges with the APOKYN Pen would be an unapproved use of the APOKYN Pen, given that the APOKYN Pen is approved only for use with the APOKYN Cartridges. An ANDA cannot be approved if it depends upon such an unapproved use of the APOKYN Pen with a generic drug product.

It is well-settled that FDA-approved labeling may not imply or suggest unapproved uses.[92] ANDA labeling that directs the patient to administer a generic apomorphine hydrochloride drug product using the APOKYN Pen would go well beyond implying or suggesting an unapproved use: it would instruct such use and the approval of the ANDA product would depend upon such use. Because the APOKYN Pen is approved "for use only with 3 mL APOKYN . . . Cartridges," no ANDA lawfully can be approved for a generic drug product

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[90] *See Premarket Pathways Draft Guidance*, at 12 (ANDAs must show that the proposed generic can be substituted for RLD with the expectation that is equivalent in terms of safety and effectiveness); *see also* 21 C.F.R. § 314.3(b) (providing the definition of an RLD).

[91] *See Technical Considerations for Pen, Jet, and Related Injectors Guidance*, at 7–9 (describing the different usage groups of injectors).

[92] *See, e.g.*, 21 C.F.R. § 201.57(c)(15)(i).

that relies upon the unapproved use of the APOKYN Pen to administer a drug product other than the APOKYN Cartridges.

4. An ANDA applicant cannot seek approval of a drug constituent part alone for use with the APOKYN Pen because the applicant will be unable to ensure CGMP compliance.

Even if it were possible for an ANDA applicant for a drug-device combination product to seek approval for only the drug constituent part for use with the RLD's device constituent part, the holder of any such approved ANDA would be unable to fulfill its obligation to ensure compliance with applicable CGMP requirements.

A generic drug product that is labeled for exclusive use with the APOKYN Pen would be a combination product consisting of drug and device constituent parts.[93] As stated by FDA, "[t]he constituent parts of a combination product retain their regulatory status (as a drug or device, for example) after they are combined. Accordingly, the CGMP requirements that apply to each of the constituent parts continue to apply when they are combined to make combination products."[94]

Combination product manufacturers are required to demonstrate compliance with all applicable CGMP regulations.[95] And FDA has made clear that the "holder of the application or clearance for the product . . . is responsible for compliance with all aspects of the CGMP requirements applicable to the *entire* manufacturing process and across all facilities."[96] This obligation applies even if the holder is not directly engaged in a constituent part's manufacture. As discussed above, FDA has recommended a variety of mechanisms for the holder to ensure CGMP compliance when it is not directly engaged in the manufacture of one or more constituent parts of the finished combination product, such as audits, access to quality-related documents, and other contractual agreements to ensure the holder's oversight and control over the manufacturing process.[97]

To further explain and emphasize these points, FDA provided the following example, in the context of a single-entity combination product, in guidance discussing CGMP requirements for combination products:

> Manufacturer A is responsible for establishing and maintaining procedures for design control activities for the combination product. In this scenario, Manufacturer A is the owner and is manufacturing the prefilled syringe. Accordingly, Manufacturer A is responsible for the design control activities for the syringe part of the combination product, as well as having overall responsibility for

[93] *See supra* note 45 and accompanying text.

[94] 78 Fed. Reg. at 4307.

[95] *See Combination Products CGMP Guidance*.

[96] 78 Fed. Reg. at 4311 (emphasis added); *see also Combination Products CGMP Guidance*, at 17.

[97] *See* section I.B.4, *supra*.

> the combination product. However, Manufacturer A is buying the syringe components from Manufacturer B, another manufacturer, which uses the same components to manufacture finished syringes. . . .
>
> An appropriate first step for Manufacturer A would be to review Manufacturer B's design control data to determine what new questions are raised by the use of the syringe with the drug, and to assess what additional design control activities may be needed as a consequence. . . . Manufacturer A must ensure that all design considerations for the combination product are addressed in accordance with 21 CFR 820.30.[98]

The holder of an ANDA for a generic version of APOKYN in which the generic cartridge is used with the APOKYN Pen would not have any relationship, contractual or otherwise, with the manufacturer of the APOKYN Pen with respect to that device, given that the APOKYN Pen is made exclusively for use as part of the APOKYN combination product.[99] Therefore, the ANDA holder would not have the ability to perform audits or require certain quality or other agreements to ensure the device manufacturer's compliance with CGMP related to the APOKYN Pen. As a result, the ANDA holder would be unable to ensure its own CGMP compliance with respect to the APOKYN Pen.

Furthermore, the ANDA holder would lack the ability to ensure coordination between the manufacturers of the generic drug constituent part and the APOKYN Pen. FDA has stated that "[m]anufacturing activities that occur at multiple facilities and associated CGMP operating systems should be coordinated appropriately. Each manufacturing facility for a combination product should have documentation specifying its respective responsibilities, and the manufacturer of the finished combination product *should have access to this documentation*."[100] Without any control over, or agreements with, the manufacturer of the APOKYN Pen with respect to that device, the ANDA holder would not have access to such documentation. To achieve the coordination necessary to ensure CGMP compliance, an ANDA applicant would need to develop its own delivery device and enter into its own agreements with the manufacturer of the delivery device.

Because the holder of a drug-only ANDA for a generic version of APOKYN would not have any relationship with the manufacturer of the APOKYN Pen with respect to that device, the holder of an ANDA for a cartridge to be used with the APOKYN Pen would be unable to ensure initial and continued compliance with its CGMP obligations with respect to the device constituent part, the APOKYN Pen. FDA has made clear that (1) proper design of a delivery device is essential to ensure safety and efficacy; (2) applicants must be able to ensure that the

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[98] *Combination Products CGMP Guidance*, at 42 (footnote omitted).

[99] Perhaps the ANDA holder might have a relationship with the device manufacturer in connection with some other product. But any control that the ANDA holder might have over the device manufacturer with respect to another product would have no bearing on whether the ANDA holder has any control over the manufacturer's production of the APOKYN Pen.

[100] *Combination Products CGMP Guidance*, at 18 (emphasis added).

delivery device is properly designed, validated, and verified; and (3) these obligations persist as long as the product remains on the market.[101] Because an improperly designed delivery device can increase the risk of overdose, underdose, or dose omissions, the lack of such assurance has clear implications for the safe and effective use of the drug. In the context of PD, improper dosing or missed treatments can exacerbate symptoms, which can negatively impact a patient's quality of life and can increase the risk of patient harm (*e.g.*, by increasing the risk of falls).[102]

5. The ANDA applicant cannot seek approval of a drug constituent part alone for use with the APOKYN Pen because it will be unable to fulfill its responsibilities related to postmarket safety reporting.

Combination products also are subject to PMSR requirements.[103] Where, as here, the combination product was approved under an NDA or ANDA, the combination product must meet the PMSR requirements in 21 C.F.R. part 314.[104] The holder of an NDA or ANDA with a device constituent part, like APOKYN, also must comply with the following PMSR requirements as they relate to the device constituent part (*i.e.*, the APOKYN Pen)[105]:

- Five-day reporting requirements;[106]
- Malfunction reporting requirements;[107] and
- Correction or removal reporting and recordkeeping requirements for events that do not require a report.[108]

For combination products marketed under an NDA with a device constituent part, the periodic safety report that is submitted under 21 CFR § 314.80(c)(2) must contain a summary and

[101] *See supra* notes 36–39 and accompanying text.

[102] *See* section I.B.1., *supra*.

[103] *See* section I.B.4, *supra*; 21 C.F.R. part 4, subpart B; *PMSR Guidance*. Although FDA does not intend to enforce certain provisions of the combination product PMSR final rule prior to certain dates in 2020 and 2021, the Agency does intend to enforce other provisions and, eventually, the Agency can be expected to enforce all provisions. The purpose of the delay in enforcement is to provide combination product applicants with sufficient time to update their reporting and recordkeeping systems and procedures to comply with the requirements. *See* FDA, *Immediately in Effect Guidance for Industry and Food and Drug Administration Staff, Compliance Policy for Combination Product Postmarketing Safety Reporting* (Apr. 2019). Given that FDA can be expected to enforce all of the PMSR requirements in later years, the concerns expressed in this section remain valid.

[104] 21 C.F.R. § 4.102(b)(2).

[105] *See id.* § 4.102(c); *PMSR Guidance*, at 8.

[106] *See* 21 C.F.R. §§ 803.3, 803.53, 803.56.

[107] *See id*. §§ 803.50, 803.56.

[108] *See id*. §§ 806.10, 806.20.

analysis of the five-day and malfunction reports that were submitted during the report interval.[109]

The holder of an ANDA for a drug cartridge to be used with APOKYN thus would be required to comply with the PMSR requirements for both the drug cartridge and the APOKYN Pen. But without any control over the device constituent part, the holder of such an ANDA would not be in a position to receive the information needed to meet its PMSR obligations.

6. The holder of an ANDA for a generic cartridge to be used with the APOKYN Pen would be unable to ensure that the generic cartridge remains compatible with the APOKYN Pen.

Another regulatory challenge associated with a generic apomorphine hydrochloride cartridge for use with the APOKYN Pen is that the ANDA holder would not be able to ensure that its generic cartridge will remain compatible with the APOKYN Pen if that device is updated in the future—even if the ANDA holder could show compatibility at the time of approval.

FDA has stated that although it is not unique to combination products, "coordination with regard to changes among manufacturers participating in the manufacture of a combination product is an important CGMP issue."[110] The Agency also has emphasized that

> Before changes are made to the manufacturing process of a constituent part, the CGMP operating system should ensure consideration of whether such changes could affect performance and/or interaction with the other constituent part(s) and, if so, whether the safety and effectiveness of the combination product could be impacted. Quality agreements with constituent part manufacturer(s) are one way to ensure that changes to a constituent part are transparent to a combination product manufacturer or owner.[111]

As discussed above, an ANDA holder without any control over or agreements with the manufacturer of the APOKYN Pen relevant to that device would lack the coordination with the device maker needed to ensure the continued compatibility of the generic cartridge and the APOKYN Pen in the future.

Additionally, to the extent that an ANDA holder needs to update its cartridge to remain compatible with a revised version of the APOKYN Pen, its ability to do so would depend upon the ANDA holder's technical capability to engineer a revised generic cartridge to be compatible

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[109] *Id*. § 4.102(d)(1).

[110] 78 Fed. Reg. at 4319; *see also Combination Products CGMP Guidance*, at 18 ("[C]oordination of changes among manufacturers participating in the manufacture of a combination product is an important CGMP issue. Appropriate consideration should be given to any implications for the safety or effectiveness of the combination product that might arise from changes to the combination product or its constituent parts.").

[111] *Combination Products CGMP Guidance*, at 17.

with the revised APOKYN Pen and to do so without infringing any applicable patents that claim the revised APOKYN Cartridge. Moreover, the ANDA holder might not be diligent in updating the generic cartridge to preserve compatibility with a revised APOKYN Pen. Under certain circumstances, therefore, there is the possibility that generic cartridges might not remain compatible with future versions of the APOKYN Pen.

Indeed, in the normal post-production design life of a device, raw material changes and part obsolescence are likely to occur that could cause changes in commercial tooling, suppliers, and facilities that could affect compatibility. As examples for APOKYN, a change in plastic resin and/or raw material for the internal spring could affect the physical features and functional characteristics of these components, which subsequently should be evaluated with the cartridge to confirm the preservation of essential performance characteristics. Likewise, a transfer of production to a new facility, supplier, or new area of a site could result in process and handling differences to the final pen components, assembly, and final functional test. Although full re-validation would occur, it would be essential to perform equivalency studies utilizing known cartridges to ensure there are no changes to system level performance (*e.g.*, dose accuracy).

With an appropriate quality agreement in place with a device manufacturer, the holder of the RLD for a combination product would have visibility into these types of changes and also would have the ability to confirm the continued compatibility of the device constituent part with its drug constituent part. A lack of compatibility could lead to medication errors, such as overdose, underdose, or dose omissions, and thus have clear implications for the safe and effective use of the product. As discussed above, the correct and timely administration of APOKYN is imperative to manage the many symptoms experienced by patients during *off* episodes and to improve patient quality of life.

7. Patient access to the APOKYN Pen for use with a generic drug product cannot be presumed.

Currently, APOKYN is the only approved drug-device combination product containing apomorphine hydrochloride and intended for use in advanced PD patients. There is no other device constituent part, branded or generic, approved for this use with an apomorphine hydrochloride drug constituent part. Nor, as noted, is there any alternative auto-injector or injector pen separately approved or cleared by FDA with technical specifications and/or intended uses compatible with this use. Accordingly, in the absence of a device constituent part proposed in an ANDA, a generic drug constituent part would need to rely upon use with the APOKYN Pen.

But it cannot be presumed that patients would have access to the RLD's device constituent part (*i.e.*, the APOKYN Pen) for use with a generic version of only the drug constituent part of the APOKYN drug-device combination product. Patients who were not previously prescribed APOKYN will not have access to the APOKYN Pen because the APOKYN Pen is dispensed by specialty pharmacies only in connection with an APOKYN prescription. For patients who have an APOKYN Pen because they were first prescribed APOKYN and then switched to a generic, there is a risk that the APOKYN Pen will break or malfunction, be lost, or

need to be replaced for some other reason (*e.g.*, general wear-and-tear).[112] If this occurs, such patients will not be able to obtain a replacement APOKYN Pen if they no longer are prescribed APOKYN. Additionally, if APOKYN is discontinued at some point, the APOKYN Pen no longer would be available even through a prescription for APOKYN.

Furthermore, if a generic version of APOKYN were approved, most insurance plans would require automatic substitution of the generic product for APOKYN unless there is a medical rationale for the patient's use of APOKYN. Therefore, if a prescriber attempts to switch a patient from a generic version to APOKYN in order to obtain an APOKYN Pen,[113] the prescriber would have to provide a medical rationale why the generic drug product would not be appropriate for the patient. This would cause a delay in the patient's access to treatment. Timely administration of apomorphine is essential to manage the symptoms of *off* episodes. But insurance-related issues could cause a delay in treatment for days or even longer.[114]

A patient's lack of access to an APOKYN Pen therefore could delay or interrupt treatment with potential clinical consequences resulting from missed or delayed doses.[115] Moreover, the need for patients to secure access to the APOKYN Pen for use with a generic drug constituent part could increase the risk that patients will share the APOKYN Pen, which the APOKYN Pen IFU explicitly state should not occur.[116] Such sharing of an APOKYN Pen would create a safety issue by increasing the risk of infection.[117]

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[112] Indeed, the APOKYN Pen IFU advise the patient to replace the APOKYN Pen if it does not work due to mechanical failure or if the dose numbers and/or other markers wear off due to repeated use over an extended period of time. APOKYN Pen Instructions for Use, at 26.

[113] As mentioned above, APOKYN Pens are provided to patients with an APOKYN prescription.

[114] *See* American Medical Association, *2018 AMA Prior Authorization (PA) Physician Survey* (2019), https://www.ama-assn.org/system/files/2019-02/prior-auth-2018.pdf (finding that PAs can leave patients waiting up to 3 days or longer to receive certain treatments, with 91% of physicians surveyed reporting care delays associated with PAs) (attached as Ex. 20).

[115] *See supra* notes 36–39, and accompanying text; *see also* Complete Response Letter from Mary H. Parks, FDA, to Mary Ann McElligott, Novo Nordisk Inc., at 2 (Aug. 20, 2010) (issuing a CRL for Novolog (insulin aspart [rDNA origin]) injection, expressing concerns about, among other things, blocked "push buttons" on a pen injector used to which could result impact the delivery of a dose of insulin) (attached as Ex. 21); Mishale Mistry, Acting Assoc. Dir., Div. of Medication Error Prevention & Analysis, FDA, *Ongoing Role of FDA in Medication Error Prevention* (discussing factors that contributed to errors related to Insulin Human Injection U-500, including "[i]naccurate dosing associated with the lack of a dedicated dosing device and poor communication of the desired dose") (attached as Ex. 22).

[116] APOKYN Pen Instructions for Use, at 4 ("The **APOKYN Pen** is only for use by 1 patient and should not be shared.").

[117] *C.f., e.g.*, Schaefer MK, Kossover RA, Perz JF, *Sharing Insulin Pens: Are You Putting Your Patients At Risk*, DIABETES CARE 2013 Nov;36(11):e188–9, e188 (2013) ("Backflow of blood and other biological material into the insulin cartridge can occur after injection. For this reason, insulin pens, like other injection devices, must never be used by more than one person.") (attached as Ex. 23); Centers for Disease Control and Prevention, *CDC Clinical Reminder: Insulin Pens Must Never Be Used for More than One Person* (Jan. 2012) (noting that the shared use of insulin pens "places individuals at risk of infection with pathogens including hepatitis viruses and human immunodeficiency virus (HIV)"), https://www.cdc.gov/injectionsafety/clinical-reminders/insulin-pens.html (attached as Ex. 24).

B. FDA should develop a policy framework establishing the circumstances, if any, under which a drug constituent part can be approved in an ANDA that does not seek approval of the device constituent part.

We are filing this petition because FDA has not clarified whether the Agency will approve in an ANDA only the drug constituent part of a drug-device combination product that is approved in an NDA. For the reasons discussed above, this type of ANDA would not be approvable as a matter of law, and could put patients at risk. We ask that FDA clearly state the Agency's position on this issue in order to reduce uncertainty for innovators, generic drug developers, and other stakeholders.

If FDA, notwithstanding the applicable legal and public health issues, determines that under some circumstances, only the drug constituent part of a drug-device combination product approved in an NDA may be approved in an ANDA, we ask that the Agency develop a policy framework to provide clarity on FDA's approach. To ensure that input from all interested stakeholders is considered, the Agency should develop this framework through a transparent, public process. As the interest in combination products continues to increase,[118] it is essential for FDA to clarify how it intends to apply the Agency's Hatch-Waxman authorities and policies to this type of combination product.

III. Response to Sage Comment

A. The Applicant's ANDA needs to seek approval of a drug-device combination product.

The Sage Comment claims that "[t]he ANDA submitted by Applicant is not . . . for a drug-device combination," but instead "is for the [drug] cartridge only."[119] But as a legal and regulatory matter, any ANDA for an apomorphine hydrochloride cartridge for use with the APOKYN Pen would need to seek approval of a combination product consisting of the generic drug constituent part and a delivery device, for two reasons.

First, there is no legal or regulatory authority for approving an ANDA for only the drug constituent part of a drug-device combination product RLD.[120]

Second, an ANDA would need to seek approval of the APOKYN Pen (or another appropriate device) for use with the generic cartridge because no device currently is legally available for use with a generic cartridge. The APOKYN Pen was approved solely for use with

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[118] *See, e.g.*, FDA, *FDA in Brief: To Advance Efficient Development and Review of Combination Products, the FDA Outlines Principles to promote a More Predictable Premarket Review Pathway* (Feb. 5, 2018), https://www.fda.gov/news-events/fda-brief/fda-brief-advance-efficient-development-and-review-combination-products-fda-outlines-principles ("Combination products present significant opportunities for improvement in patient care.") (attached as Ex. 25).

[119] Sage Comment, *supra* note 3, at 4, 6.

[120] *See, e.g.*, King Petition Response, *supra* note 60, at 6 (stating that in reviewing an ANDA that references a combination product, FDA "considers the RLD as a whole and its individual constituent parts"); *see also* section II.A.1, *supra*.

the APOKYN cartridge under the APOKYN NDA. This is reflected in the APOKYN Pen IFU that refers only to the APOKYN cartridge and not to any generic product. The APOKYN Pen IFU's reference to the APOKYN cartridge cannot reasonably be construed to include generic products. Just as FDA requires that Risk Evaluation and Mitigation Strategies (REMS) be modified to reflect a broadening of their scope to include both the innovator and generic products, so too must the APOKYN Pen IFU be updated to reflect the addition of an indication for use with the generic drug product.[121]

Such an update to the device labeling requires regulatory action by FDA. Insofar as the ANDA applicant would seek to include the APOKYN Pen in its ANDA for use with the generic cartridge, we are not aware of any legal or regulatory authority for the approval of an ANDA seeking approval of a device constituent part made by a company with whom the ANDA applicant lacks any relationship. And, as discussed above, even if it were legally possible for an ANDA applicant to submit such an application, the lack of any relationship between the ANDA applicant and the manufacturer of the APOKYN Pen would create challenges for the ANDA applicant with respect to CGMP compliance and postmarket safety reporting for the combination product approved under the ANDA, as well as ensuring the continued compatibility of the generic cartridge and the APOKYN Pen, as detailed above.[122] These considerations are essential to the safety and efficacy of any generic cartridge for patients. Additionally, it cannot be presumed that patients would have continued access to the APOKYN Pen for use with a generic cartridge.[123]

We note that the challenge of maintaining compatibility between a generic cartridge and the APOKYN Pen is not merely hypothetical. Future changes to the APOKYN Pen are in development at this time as a requirement imposed by US WorldMeds' suppliers to maintain the economic viability of APOKYN Pen production. Planned changes to the APOKYN Pen will require changes to the APOKYN cartridge to maintain compatibility and US WorldMeds is working closely with the pen manufacturer to design and validate the system in consideration of both the drug and device constituent parts, as required by each party's design control procedures. The timely coordination of changes to the drug and device constituent parts and notification to customers are made possible by the commercial relationship between US WorldMeds and the manufacturer of the APOKYN Pen.

This planned change to the combination product system and the need for ongoing coordinated efforts to produce both the drug and device constituent parts illustrate why distributing the APOKYN Pen for use with generic cartridges would undermine important change control and design control procedures required for the compliant marketing of combination products. In this specific example, once the next-generation APOKYN Pen and cartridge are introduced, the prior version of the APOKYN Pen no longer will be distributed.

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[121] *See, e.g.*, FDA, *Guidance for Industry*, *Risk Evaluation and Modification Strategies: Modifications and Revisions*, at 9 (Rev. 1, July 2019) (identifying as a major REMS modification "[c]hanging a REMS for an individual product to [a shared system] REMS.").

[122] *See* sections II.A.4, II.A.5, II.A.6, *supra*.

[123] *See* section II.A.7, *supra*.

This could lead to an interruption in treatment for a patient using the generic cartridge that is compatible with a prior-generation APOKYN Pen.

Finally, it is not true, as the Sage Comment claims, that the challenges presented by the lack of a relationship between the ANDA applicant and APOKYN Pen manufacturer suggest that "no product ever administered by a device, including a needle injection, could ever be approved, unless the NDA or ANDA applicant also manufactured the device."[124] These concerns arise solely because the ANDA applicant would be seeking approval of a drug-device combination product in the ANDA (giving rise to the relevant CGMP and postmarket safety reporting obligations with respect to the device constituent part), and the ANDA applicant would lack any coordination with or control over the device manufacturer. By contrast, these concerns would not arise if the ANDA applicant were not seeking approval of a combination product (because, for example, the drug product can be used with a general-use device like a syringe), or if the ANDA applicant were to propose a combination product with a device constituent part made by the ANDA applicant or a manufacturer with whom the ANDA applicant has a commercial relationship.

B. The ribavirin ANDA is not a relevant precedent because the drug and device constituent parts for VIRAZOLE® are the subjects of separate applications.

The Sage Comment claims—incorrectly—that a "long standing FDA policy" supports approval of an ANDA for only the drug constituent part of APOKYN (i.e., an apomorphine hydrochloride cartridge) for use with the APOKYN Pen.[125] As evidence of such a policy, the Sage Comment cites FDA's approval in 2016 of an ANDA for ribavirin for inhalation solution to be used with the same delivery device as the RLD (VIRAZOLE® (ribavirin)).[126]

There is no such "long standing FDA policy" on the approvability of an ANDA for only the drug constituent part of a drug-device combination product approved in a single application. If there were such a policy, this petition, like other recent petitions that raised similar issues, would not have been necessary.[127]

Nor is the ribavirin example directly relevant to the issues addressed by this petition. Unlike the drug and device constituent parts in the APOKYN combination product, VIRAZOLE and its delivery device—the Small Particle Aerosol Generator (SPAG-2) nebulizer—were not approved in a single marketing application. Instead, the ribavirin constituent part was approved

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[124] Sage Comment, *supra* note 3, at 5.

[125] *Id*.

[126] In one place, the Sage Comment refers to Navinta LLC's ANDA 207366 for ribavirin for inhalation solution. *Id*. at 3. Elsewhere, the Sage Comment refers to Zydus's ANDA 077094 for ribavirin oral tablets. *Id*. at 5, 7. We presume that the references to ANDA 077094 are in error because the oral tablets do not require a device for administration.

[127] *See, e.g.*, Citizen Petitions Submitted on Behalf of United Therapeutics Corp. re: TYVASO® (treprostinil), Docket Nos. FDA-2016-P-0187, FDA-2016-P-2478, FDA-2017-P-2162, FDA-2017-P-5477, FDA-2018-P-0598, FDA-2018-P-2659.

in new drug application (NDA) 18859 and the device constituent part was cleared in 510(k) K843717.

Because the drug and device constituent parts for VIRAZOLE are the subjects of separate marketing applications, it was possible for the ANDA to identify only the VIRAZOLE drug product as the RLD and cross-label the drug to a separately cleared or approved device. By contrast, both the drug and device constituent parts of APOKYN —the APOKYN cartridge and APOKYN Pen, respectively—were approved in a single marketing application, NDA 021264. Both constituent parts of APOKYN therefore comprise the RLD. To approve an ANDA for only the drug constituent part, FDA would need to allow the applicant to subdivide the RLD into drug and device constituent parts in the absence of any legal or regulatory authority for that approach.[128]

Additionally, in the ribavirin example, the Agency apparently considered the SPAG-2 nebulizer's indication for use with VIRAZOLE to also include the generic ribavirin product, obviating the need for additional regulatory action by FDA with respect to the device. Further, FDA apparently concluded that the device that was separately cleared and legally available to be cross-referenced in the ANDA labeling. Here, by contrast, even assuming that the APOKYN Pen's indication for use with APOKYN also would cover use with the generic cartridge, there is no device constituent part approved or cleared under device authorities to which the Applicant's generic cartridge could be cross-labeled. The APOKYN Pen legally exists only as a device constituent part of the APOKYN combination product approved under an NDA. We are not aware of any authority or precedent that establishes the permissibility of cross-labeling a generic drug product to a device constituent part approved in an NDA.

And, finally, the ribavirin ANDA did not face the challenges in complying with the "same labeling" requirement that the Applicant's ANDA would encounter. Because the SPAG-2 device was separately cleared, its Instructions for Use (IFU) are not part of the labeling approved under the VIRAZOLE NDA.[129] By contrast, the labeling approved under the APOKYN NDA includes the IFU for both the drug and the APOKYN Pen.[130] Given that the Applicant claims to seek approval of the cartridge alone, we presume that the Applicant seeks to omit the APOKYN Pen IFU from the generic product's labeling to be approved under the ANDA. But it is unclear how the Applicant's proposed labeling would satisfy the statutory requirement that the generic product and RLD (here, the APOKYN drug-device combination product) share the same labeling.[131] Nor is it apparent how the omission of the APOKYN Pen IFU from the ANDA

[128] *See* note 120, *supra*.

[129] *See* VIRAZOLE Prescribing Information (May 2019) (attached as Ex. 26).

[130] *See supra* note 4.

[131] FDCA § 505(j)(2)(A)(v).

labeling would be a permissible labeling difference that results from the production or distribution of the generic product and RLD "by different manufacturers."[132]

Nonetheless, the ribavirin example cited by Sage raises questions about FDA's approach to the approvability of an ANDA for only the drug constituent part of a drug-device combination product. The ribavirin example seems to suggest that a device constituent part approved for use only with the innovator's drug product (as opposed to a general use device) also can be indicated for use with a generic drug product, without the need for additional regulatory action with respect to the device. If so, where a separately cleared or approved device exists, the generic drug manufacturer would be able to cross-label its generic drug product with the cleared or approved device, making the device a constituent part of a new combination product. The device manufacturer (in the ribavirin example, the SPAG-2 manufacturer) would automatically, and without choice, become responsible for the device constituent part of the new generic drug product-device combination product, and would be required to share postmarket safety information with the generic drug manufacturer.[133] In this way, additional regulatory obligations would be imposed upon the manufacturer of the device constituent part of a combination product without that device manufacturer seeking to market the device constituent part as part of the new combination product. It seems unlikely that FDA intended this outcome.

C. <u>This petition was submitted for appropriate purposes.</u>

Finally, there is no merit to the allegation in the Sage Comment that this petition was submitted for inappropriate purposes.[134]

The assertion that US WorldMeds has acted to "restrict patient access to lower cost medication and limit supply" is particularly baseless. We devote substantial resources to support the safe and effective use of APOKYN in the very small population of patients who take this product. For example, we provide a network of nearly 40 clinical nurse educators across the country who provide direct, usually in-home, training for patients and caregivers to properly use the APOKYN Pen, consistent with the following direction in the APOKYN labeling: "Do not use the APOKYN® Pen unless you and your care partner have been taught the right way to use it and both of you understand all of the instructions."[135] This program and other additional patient education resources cost US WorldMeds nearly $10 million per year. This may appear to be a disproportionately large investment relative to the small patient population using APOKYN today, but it is supported because of the need to provide patients and their caregivers appropriate educational support, training, and individually optimized dosing. This is especially important to APOKYN patients given the unique challenges of Parkinson's disease and the benefits of effective management of *off* episodes.

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[132] *Id.*; *see also* 21 C.F.R. §§ 314.94(a)(8)(iv), 314.127(a)(7).

[133] *See* 21 C.F.R. § 4.103.

[134] Sage Comment, *supra* note 3, at 3, 7.

[135] APOKYN Pen Instructions for Use, at 4.

Similarly, the claim that US WorldMeds can "make the pen available to" patients taking the generic product reflects an apparent lack of understanding of the commercial challenges associated with developing a low-volume device like the APOKYN Pen and securing a reliable supply. Indeed, if we were to give away the APOKYN Pen for use with a generic cartridge, it would not be financially viable for US WorldMeds to continue to provide the existing level of support to patients, and it might be challenging to continue distribution of APOKYN at all.

The suggestion that we can "facilitate[]" coordination between the ANDA applicant and device manufacturer to ensure continued compatibility likewise overlooks the practical challenges that would result, given the absence of any commercial relationship between the ANDA applicant and the device manufacturer.[136] And there is no merit to the suggestion that changes to the APOKYN Pen would be made for an improper purpose.[137] The APOKYN Pen contract manufacturer is making design changes to the device that require US WorldMeds to evaluate continued compatibility with and make necessary changes to the drug constituent part in order to make the production of this low-volume device financially viable for the device manufacturer. This type of change imposed by a supplier's demands is commonplace in the pharmaceutical industry and does not reflect any inappropriate purpose. Rather, changes may be required by suppliers' business strategies, part and equipment obsolescence, and/or manufacturing efficiencies necessary for the economic viability of a contract manufacturer.

In sum, FDA's regulatory framework is intended to ensure the safety, efficacy, and manufacturing quality of drug and device products, whether or not they are approved as constituent parts of a combination product.[138] This petition is intended to encourage FDA to develop a policy framework that would achieve this goal with respect to certain ANDAs that reference combination products. In developing such a policy framework and applying it to an ANDA referencing APOKYN, we ask that FDA consider that the proper operation of APOKYN's drug and device constituent parts with each other is critical to ensuring that patients' symptoms of Parkinson's disease are managed safety and effectively.

IV. Conclusion

For the foregoing reasons, FDA should require that any ANDA referencing APOKYN seek approval of generic versions of both the drug and device constituent parts of APOKYN. The Agency also should establish a policy framework clarifying the circumstances, if any, under which the drug constituent part of a generic drug-device combination product can be approved in an ANDA that does not also seek approval of the device constituent part.

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[136] Sage Comment, *supra* note 3, at 6.

[137] *Id*.

[138] *See, e.g.*, 78 Fed. Reg. 4307, 4319 (Jan. 22, 2013) (stating that FDA's combination product regulations do not "relax[] CGMP requirements," but instead provide "a more efficient means to satisfy them.").

C. Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted only upon the request of the Commissioner.

E. Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: April 24, 2019. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: I am making these representations on behalf of US WorldMeds as part of my responsibilities as an employee of US WorldMeds; I am not being separately compensated for submitting this petition. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

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