


RESEARCH ARTICLE

The US Food and Drug Administration's tentative approval process and the global fight against HIV

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Abstract

Introduction: In 2004, the US government began to utilize the Food and Drug Administration's (USFDA) tentative approval process (tFDA) as a basis to determine which HIV drugs are appropriate to be purchased and used in resource-constrained settings. This process permits products that are not approved for marketing in the US, including medicines with active patents or marketing restrictions in the US, to be purchased and distributed in resource-constrained settings. Although the tFDA was originally intended to support the United States' President's Emergency Plan for AIDS Relief (PEPFAR), the USFDA list has become a cornerstone of international HIV programmes that support procurement of ARVs, such as the World Health Organization and the Global Fund to Fight AIDS, Tuberculosis, and Malaria. Our objective in this article is to help the global HIV policy makers and implementers of HIV programmes better understand the benefits and limitations of the tFDA by providing an in-depth review of the relevant legal and regulatory processes.

Discussion: USFDA's dedicated tFDA process for ARVs used by the PEPFAR programme has a wide impact globally; however, the implementation and the regulatory processes governing the programme have not been thoroughly described in the medical literature. This paper seeks to help stakeholders better understand the legal and regulatory aspects associated with review of ARVs under the tFDA by describing the following: (1) the tFDA and its importance to global ARV procurement; (2) the regulatory pathways for applications under tFDA for the PEPFAR programme, including modifications to applications, review timelines and costs; (3) the role of US patents, US marketing exclusivity rights, and the Medicines Patents Pool in tFDA; and (4) an overview of how applications for PEPFAR programme are processed through the USFDA. We also provide a case study of a new ARV, tenofovir alafenamide fumarate (TAF), not yet reviewed by USFDA for PEPFAR use.

Conclusions: In this paper, we describe the importance and implementation of USFDA's tentative approval process to review ARVs for resource-constrained settings. We also highlight the impact of patents and exclusivities on review of HIV drugs under tFDA and illustrate the concepts using a new HIV drug as an example.

Keywords: HIV; AIDS; PEPFAR; Global Health; FDA; USFDA; tentative approval; TAF

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1 | INTRODUCTION

In 2016, an estimated 37 million people were living with HIV, 17 million of whom had access to antiretroviral (ARV) therapy [1]. Many of the 17 million gain access to care, at least in part, through global programmes such as the President's Emergency Plan for AIDS Relief (PEPFAR). Treating such a large number of patients is human resource-intensive, which is further complicated by the high cost of drugs. PEPFAR was launched in 2003 to help get affordable treatment to persons with HIV worldwide and is permitted by US law to purchase medicines that have been quality-assured by the US Food and Drug Administration (USFDA) [2,3].

To help PEPFAR achieve its goals, in 2004 the USFDA implemented a dedicated process to review ARVs for potential purchase utilizing PEPFAR funds, using, in those situations where full approval could not be granted in the United States because of patents or market exclusivity, a pre-existing tentative approval process (tFDA). Another mechanism, the World Health Organization's (WHO) Prequalification of Medicines Programme (PQP), was also available in 2004 to ensure quality of ARVs, and was proposed for use by PEPFAR. However, a decision was made by the US Department of State that any medicines purchased with US government funds would meet the same standards as those sold in the US, and thus the US government opted for the use of tFDA [4]. The tFDA ensures

that only ARVs that have been shown to be safe and effective and meet US standards for quality are available for patients who obtain ARVs through PEPFAR funding. USFDA facilitates the use of tFDA for this purpose by creating a publicly available list of quality-assured ARVs.

While originally intended to support the United States' PEPFAR programme, this list has become a cornerstone of international HIV procurement programmes. The WHO, the Global Fund to Fight AIDS, Tuberculosis, and Malaria (the Global Fund), and other global entities have come to utilize the list of ARVs registered through the tFDA to guide procurement of HIV drugs (Figure 1). We use here the term "registered" to refer to ARVs approved or tentatively approved by USFDA; this should not be confused with the requirement of registration of manufacturing facilities and listing of drug products that is required for all drugs distributed in the US.

To encourage manufacturers' participation in the tFDA, USFDA has conducted direct outreach to drug manufacturers in China and India to describe the process and application requirements. However, the regulatory processes governing the programme have not been thoroughly described in the medical literature for other stakeholders, such as policy makers and HIV programme implementers, who want to better understand the benefits and limitations of the tFDA. The objective of this paper is to help stakeholders better understand the legal and regulatory aspects associated with review of ARVs under the tFDA. To accomplish this, we describe: (1) the tFDA and its importance to global ARV procurement; (2) the regulatory pathways for applications under tFDA for the PEPFAR programme, including modifications to applications, review timelines and costs; (3) the role of US patents, US marketing exclusivity rights, and the Medicines Patents Pool on tFDA; and (4) a high-level overview of how applications for the PEPFAR programme are processed through the USFDA. Finally, this paper provides a case study of a new ARV not yet registered through tFDA for PEPFAR use.

2 | DISCUSSION

2.1 | What is the tFDA and what is its relevance to global procurement of ARVs?

A tentative approval (TA) is issued to drugs that cannot be approved for marketing in the United States because of patents or exclusivities related to the reference drug product (e.g. brand name drug) on which they rely for approval [5]. Many tentatively approved ARVs are generic drugs, which are identical copies, except for differences permitted by USFDA regulations, of already USFDA-approved drugs [6]. Some are new versions of previously approved ARVs such as fixed-dose combinations or new strengths or formulations that are designed for ease of use or for children [7,8]. An application seeking TA is reviewed by the USFDA using the same criteria for safety, efficacy and quality as any other drug. Tentatively approved products, however, cannot be sold in the United States due to existing patents and/or exclusivities on the product (discussed below) and final approval for the US market is postponed until such barriers have been addressed [5]. The drugs, however, can still be purchased for use in the high prevalence, resource-constrained countries that partner with PEPFAR, the Global Fund or other similar programmes.

A key advantage of the tFDA designation is that the ARVs reviewed under this process are likely to be considerably less expensive than their brand name counterparts [9]. This price advantage allows PEPFAR and other procurement entities to purchase greater quantities of life-saving medicines and as a result, the tFDA has been a key factor in the success of PEPFAR treatment initiatives [10,11]. Since the beginning of the programme, USFDA has registered a total of 241 ARV products (including different strengths and formulations from different manufacturers of the same product version) through 191 distinct applications for use by PEPFAR. Of these, 221 were still available (i.e. currently in tentatively approved or approved regulatory standing with the USFDA) for PEPFAR procurement as of 10 January 2017. While PEPFAR may use any ARV product approved by the USFDA, including the more than 100 innovator and generic products that are not approved pursuant to the PEPFAR programme, these are not the focus of this paper [12]. In 2016, using USFDA-registered products, PEPFAR supported the treatment of 11.5 million HIV patients through 28 country and regional programmes [11,13].

To promote greater availability of combination ARV therapies that are easier to distribute and administer under PEPFAR, USFDA issued guidance for industry in 2006 to encourage the development of new fixed dose combinations and co-packaging of existing ARVs [7]. The guidance provided a list of ARVs that could be supported by existing efficacy and safety data. Applicants would have to supplement these data with quality and bioequivalence testing, but new lengthy and costly clinical trials were no longer deemed necessary. Thus far, this has led to approval of 38 new combinations, strengths and formulations of existing ARVs that are not yet available in the US (Table 1), resulting in 86 products (out of the 241 drugs approved for PEPFAR), of which 74 are currently available. Twenty-one of these new combinations, strengths or formulations (55%) are for paediatric use.

2.2 | What is the regulatory process for applications used by the PEPFAR under the tFDA?

In this section we describe: (1) the regulatory pathways used by PEPFAR tFDA applications; (2) how those applications are modified; (3) how long it takes to review the applications; and (4) the fees associated with PEPFAR tFDA applications.

2.2.1 | Regulatory pathways

First, we explore how to employ USFDA's regulatory pathways for review of applications under the tFDA used by PEPFAR. The ARVs used by the PEPFAR programme are reviewed under the same three standard regulatory pathways that USFDA uses for the review of all drugs. The three pathways (named after the statutes in the Food, Drug, and Cosmetic Act) are 505(b)(1), 505(b)(2), and 505(j) and are discussed below, along with their relevance to PEPFAR [14]. Figure 2 depicts the overall process for receiving and reviewing drug applications for the PEPFAR programme. The **case study** (at the end of the paper) provides an example of how the tFDA process may be used for a particular drug.

An original New Drug Application (NDA) follows the 505(b)(1) pathway – which is used for new chemical entities or

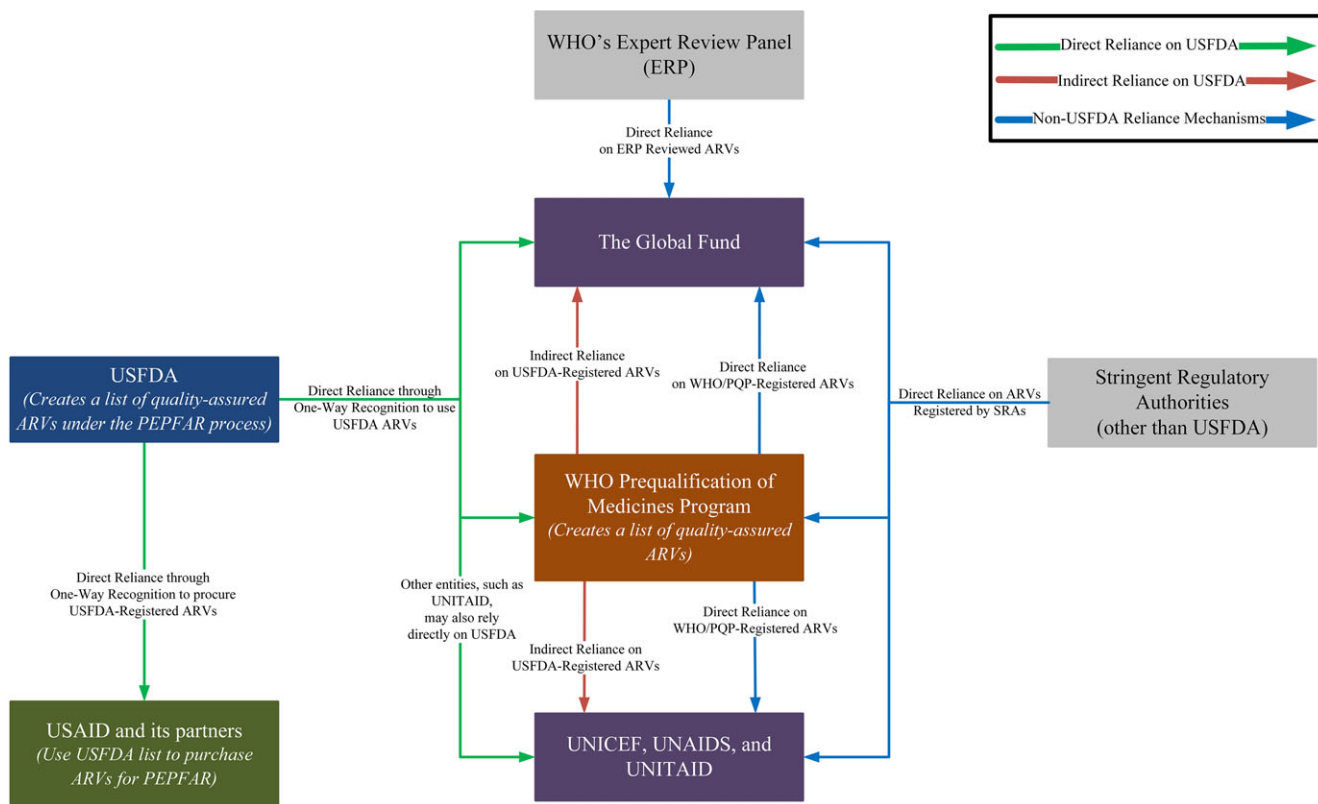


Figure 1. High-level overview of how the USFDA registrations of ARVs for PEPFAR are used by global actors. The figure shows how USFDA registrations for PEPFAR both directly and indirectly support procurement of ARVs by various global actors. The process starts when USFDA receives a product application for review under the tFDA process (blue box). If the product meets USFDA standards for safety, efficacy and quality, it is added to the list of quality-assured ARVs that can be purchased utilizing the United States' PEPFAR funds by USAID and its partners (green box). In addition, the WHO selectively places some of the USFDA registered ARVs on its quality-assured prequalification of medicines list (orange box). ARVs on the United States tFDA list and/or the WHO list may be procured by various international agencies (e.g. the Global Fund, UNICEF, UNAIDS, UNITAID) that purchase medicines for HIV treatment programmes (purple boxes). In addition to USFDA, The Global Fund, WHO, and United Nations entities may rely on other stringent regulatory authorities for quality assurance and the Global Fund may, in limited circumstances, use WHO's Expert Review Panel (grey boxes). USFDA, US Food and Drug Administration; PEPFAR, President's Emergency Plan for AIDS Relief; ARV, antiretroviral; USAID, US Agency for International Development; WHO, World Health Organization.

innovator products. This pathway requires the full range of clinical and non-clinical pharmacology and toxicology, as well as safety and efficacy studies. This pathway can also be used for changes to the drug by the innovator company or another applicant if it has the right to reference the original information [7]. To date, this pathway has not been employed by PEPFAR applicants. However, a drug approved under the 505(b)(1) pathway can be used as a reference for new combinations, formulations and generic drug applications under the 505(b)(1) pathway or in the context of PEPFAR, under the 505(b)(2) or 505(j) pathways, as discussed below. For example, if the applicant of the innovator product chose to modify the original drug that was approved under 505(b)(1), it would still use the 505(b)(1) pathway for the modification because the applicant has the right to use information from the original application.

If an applicant does not have right of reference to the original NDA data or any additional data needed to support the application, an application for a new drug can proceed through the 505(b)(2) pathway [7]. This pathway relies on the USFDA

finding that innovator products approved under the 505(b)(1) pathway are safe and effective and thus permits the applicant to proceed without duplicating the safety and effectiveness data that supported approval of the innovator application. This is a common and versatile pathway for tFDA applications used by PEPFAR, as it allows the applicants to combine the individually approved active ingredients in a single tablet or co-package multiple USFDA-approved innovator products without having to conduct the entire spectrum of clinical and non-clinical studies [7]. The resulting combinations and co-packaged drugs make HIV treatment simpler for prescribers and patients. Thus far, all NDAs registered for PEPFAR by the USFDA have followed this pathway (75 applications resulting in 88 ARVs) [15].

The 505(j) pathway is used for Abbreviated New Drug Applications (ANDA). ANDAs are for generic drug applications that do not need new clinical or pre-clinical studies. ANDAs can be approved if they establish that the drug is therapeutically equivalent to the reference product (e.g. the innovator drug). A determination that a drug product is therapeutically

Table 1. Available innovative ARV combinations and formulations registered through USFDA's tentative approval programme for PEPFAR (January 2017)

Population	Drug type	Drug name	Strength (mg)	Dosage form	No. of registered products
Adult	2 Drugs FDC	Atazanavir + Ritonavir	300 + 100	Tablet	2
		Lamivudine + Stavudine	150 + 30	Tablet	4
			150 + 40	Tablet	1
	3 Drugs FDC	Lamivudine + Tenofovir DF	300 + 300	Tablet	6
		Efavirenz + Lamivudine + Tenofovir DF	600 + 300 + 300	Tablet	4
		Lamivudine + Nevirapine + Stavudine	150 + 200 + 30	Tablet	4
			150 + 200 + 40	Tablet	2
		Lamivudine + Nevirapine + Zidovudine	150 + 200 + 300	Tablet	6
		Co-Packaged	[Atazanavir + Ritonavir] + [Lamivudine + Zidovudine]	[300 + 100] + [150 + 300]	Tablet
	[Emtricitabine + Tenofovir DF] + Nevirapine		[200 + 300] + 200	Tablet	1
	[Lamivudine + Stavudine] + Efavirenz		[150 + 40] + 600	Tablet	1
	[Lamivudine + Stavudine] + Nevirapine		[150 + 40] + 200	Tablet	1
	[Lamivudine + Tenofovir DF] + Nevirapine		[300 + 300] + 200	Tablet	2
			[300 + 300] + 200	Tablet	1
	[Lamivudine + Zidovudine] + Abacavir		[150 + 300] + 300	Tablet	1
	[Lamivudine + Zidovudine] + Efavirenz		[150 + 300] + 600	Tablet	3
[Lamivudine + Zidovudine] + Nevirapine	[150 + 300] + 200		Tablet	3	
Paediatric	Single drug	Abacavir	60	Tablet	1
				Tablet, oral suspension	1
		Efavirenz	50	Tablet	1
			100	Tablet	1
			200	Tablet	2
		Nevirapine	50	Tablet, oral suspension	2
			100	Tablet, oral suspension	1
		Ritonavir	25	Tablet	1
			50	Tablet	1
		Zidovudine	100	Tablet	1
	2 Drugs FDC	Abacavir + Lamivudine	60 + 30	Tablet	3
				Tablet, oral suspension	2
			120 + 60	Tablet, oral suspension	1
		Lamivudine + Stavudine	30 + 6	Tablet, oral suspension	1
			60 + 12	Tablet, oral suspension	1
		Lamivudine + Zidovudine	30 + 60	Tablet	3
		Tablet, oral suspension	2		
3 Drugs FDC	Lopinavir + Ritonavir	40 + 10	Pellets, oral	1	
	Lamivudine + Nevirapine + Stavudine	30 + 50 + 6	Tablet, oral suspension	1	
		60 + 100 + 12	Tablet, oral suspension	1	
	Lamivudine + Nevirapine + Zidovudine	30 + 50 + 60	Tablet, oral suspension	3	
Total					74

Tenofovir DF, Tenofovir Disoproxil Fumarate; USFDA, US Food and Drug Administration; PEPFAR, President's Emergency Plan for AIDS Relief; ARV, antiretroviral.

equivalent means that the USFDA has concluded that a drug that is the subject of an ANDA is: (1) safe and effective; (2) a pharmaceutical equivalent of the reference product; (3) adequately labelled; (4) manufactured in compliance with Current Good Manufacturing Practice regulations; and (5) bioequivalent to the reference product [16]. A drug product that is therapeutically equivalent can be expected to perform

in the same manner and is comparable to the innovator product in active ingredient; it has the same dosage form, same strength, same route of administration, labelling, quality, performance characteristic and intended use [17]. The 505(j) pathway is the most common pathway for drugs used by PEPFAR, resulting in registration of 153 ARVs under 116 applications [15].

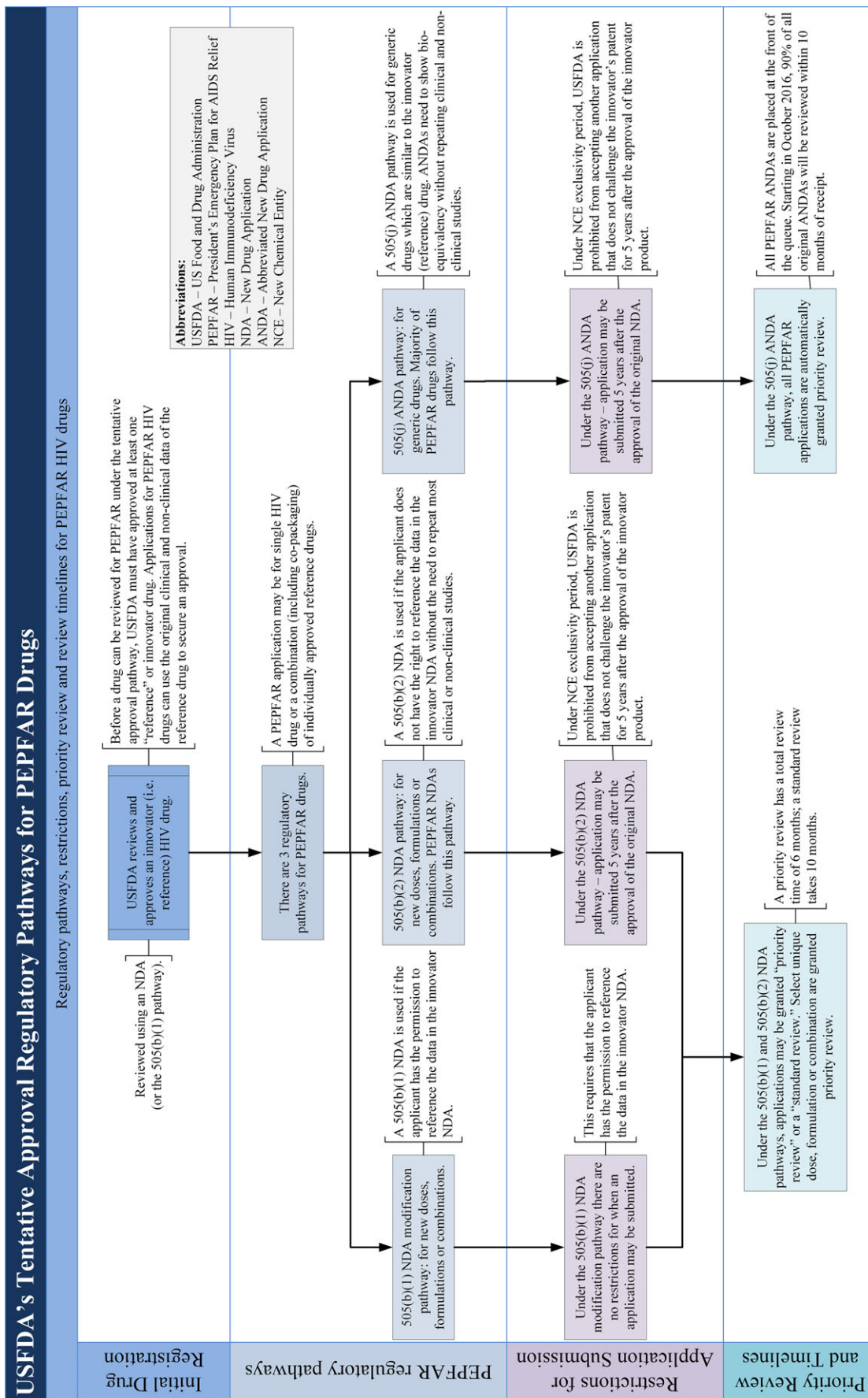


Figure 2. Infographic of USFDA's tentative approval regulatory pathways for drugs used by PEPFAR, as well as, legal restrictions, and timelines. The infographic depicts (from top to bottom) the overall process for receiving and reviewing an application for PEPFAR. The process is divided horizontally into four distinct processes: Process 1 – initial drug registration for the innovator product(s) that serve as the reference for drugs used by PEPFAR; Process 2 – the various regulatory pathways available for PEPFAR; Process 3 – legal restrictions and considerations for tFDA application submission for PEPFAR programme; and Process 4 – determination of priority versus standard reviews and related review timelines. USFDA, US Food and Drug Administration; PEPFAR, President's Emergency Plan for AIDS Relief.

2.2.2 | Modifications to applications under tFDA

After a drug for PEPFAR use has been approved under one of these three pathways, changes to the application may be submitted to USFDA [18]. These changes include the addition of a new manufacturing site, change in general manufacturing processes, extensions of shelf-life from what was originally authorized, and updated labelling or other relevant drug information [18]. Significant changes must be submitted to USFDA in a supplement to the approved application [18]. In some cases, changes cannot be made without prior USFDA approval, but in others changes can be made without waiting for USFDA approval, or even without prior notification to USFDA so long as they are reported in annual reports to the Agency [18]. What requirements apply depend on whether the changes are considered to be major, moderate, or minor [18]. Whether a change is classified as major, moderate or minor depends on the potential adverse impact the change may have on the identity, strength, quality, purity, or potency of a drug product [18].

When an application is only tentatively approved, changes must be submitted to USFDA as amendments to the ANDA or 505(b)(2) application. For drugs reviewed under the tFDA, USFDA reviews those amendments and notifies the applicant whether or not the change is permitted under the TA. If the change is not permitted, a deviation from the original TA would mean that the application would lose its TA status. For both application types, an action (permitted or denied) letter is sent to the applicant. If a denied letter is sent, USFDA may allow the applicant to continue distribution of the product if it has been already distributed, and works with the applicant to resolve pending issues. Since the beginning of the programme, USFDA has received about 1800 supplements and amendments to tFDA applications, of which about 1400 were for manufacturing changes and the remainder for labelling changes. Of these, about 82% have been approved or permitted, with 10% withdrawn, about 2% denied, and the remainder are pending review.

2.2.3 | Review times for tFDA applications

Timelines for review of applications under tFDA vary by the type of application. NDAs for the PEPFAR programme can be reviewed as either “standard” or “priority” applications [7]. By statute, 90% of all standard applications submitted to the USFDA are supposed to be reviewed within 10 months, while 90% of priority applications are to be reviewed within six months [7,19]. The applicant must request priority review, and USFDA may decide to grant priority review if one of two factors is present: (1) two or fewer drug products of the same formulation have been previously registered for PEPFAR use; or (2) on a case-by-case basis, based on public health or clinical needs. Thus far, 40% of the NDAs reviewed under the PEPFAR program have been granted priority review.

All ANDAs submitted pursuant to the PEPFAR programme get a priority review [20]. Although there are no established timelines for priority review of ANDAs submitted on or prior to 30 September 2017, under the Generic Drug User Fee Amendment (GDUFA I), 90% of all original ANDAs submitted between 1 October 2016 and 30 September 2017, including tFDA applications, should be reviewed within ten months of receipt [21]. Original PEPFAR ANDAs submitted to USFDA

after 1 October 2017 will be subject to the review timelines of the GDUFA II (second iteration of GDUFA I) agreement. Under GDUFA II, new original ANDAs, including PEPFAR ANDAs, may formally be designated for priority review with completion of the review expected within eight months, provided that certain criteria are met. Regardless of whether an original ANDA is subject to GDUFA I or GDUFA II review timeframes, the reviews of all ANDAs which identify themselves as PEPFAR applications are prioritized in some manner with the only difference being defined timelines.

The supplements or amendments for NDAs are reviewed according to established timelines, which vary by the type of change (major, moderate, or minor) [22]. Beginning October 2017, timelines will be used to review modifications to PEPFAR ANDAs [23].

2.2.4 | Fees for tFDA applications

By law, USFDA charges applicants set fees related to the cost of reviewing drug applications, facility inspections or other review-related activities. The two relevant laws for PEPFAR programme NDA and ANDAs are the Prescription Drug User Fee Act (PDUFA) and GDUFA, respectively [24,25]. For PEPFAR NDAs, USFDA may waive the application fees on a case-by-case basis to protect public health and remove barriers to innovation, and has done so for all NDAs submitted for PEPFAR use to date [7,26]. The USFDA is reimbursed for the

Table 2. Types and durations of drug exclusivities recognized by the USFDA

Exclusivity Name	Duration of exclusivity	Description	Impact on date when PEPFAR submissions can be made?
New Chemical Entity	Five years	New, never before approved molecule	Yes
Orphan Drug Entity	Seven years	For a product approved for a rare disease	No
3-Year Exclusivity	Three years	Added to an existing drug exclusivity for a previously approved molecule as a result of applicable new clinical investigations	No
Paediatric Exclusivity	Six months	Added to the end of all existing exclusivities and patent periods	Yes if added to new chemical entity exclusivity, otherwise No

USFDA, US Food and Drug Administration; PEPFAR, President's Emergency Plan for AIDS Relief.

waived fees by the US Department of State, which is responsible for coordinating PEPFAR implementation across the US government. For ANDAs submitted on or after 1 October 2012, the applicants must pay the relevant fees because USFDA does not have legal authority to waive GDUFA fees for PEPFAR programme applications [25]. For fiscal year 2017, the application fees are about \$2 million for 505(b)(1) NDAs, \$1 million for 505(b)(2) NDAs, and \$70,480 for ANDAs [24,25]. Other fees, such as Drug Master File fee, product fee, facility or establishment fees, and application amendment or supplement fees, may also apply depending on the application type and drug product [24,25].

2.2.5 | Post-tFDA safety, efficacy, or quality issues and removal of products registered under tFDA

USFDA follows the same standards for post-tFDA actions for products used by PEPFAR as it would for an approved product marketed in the US. If concerns over a product's safety, efficacy, or quality are raised for products used by PEPFAR, USFDA

investigates the issue and takes appropriate actions. Such actions may include removing the product from active regulatory status, in which case USFDA will inform US Agency for International Development (USAID), the US Department of State, and other affected stakeholders of its decision. Based on the USFDA regulatory decision, the procurement partners may stop purchasing the product in question until all issues have been resolved and the product regains its active regulatory status.

2.3 | What are the impacts of US patents, marketing exclusivity rights, and the medicines patents pool on tFDA?

2.3.1 | US patents and marketing exclusivities and their impact on tFDA

In the previous section, we explored the regulatory pathways relevant for tFDA; in this section we look at how patents and exclusivities may affect tFDA applications. In addition to prohibiting the approval of competing products in the United

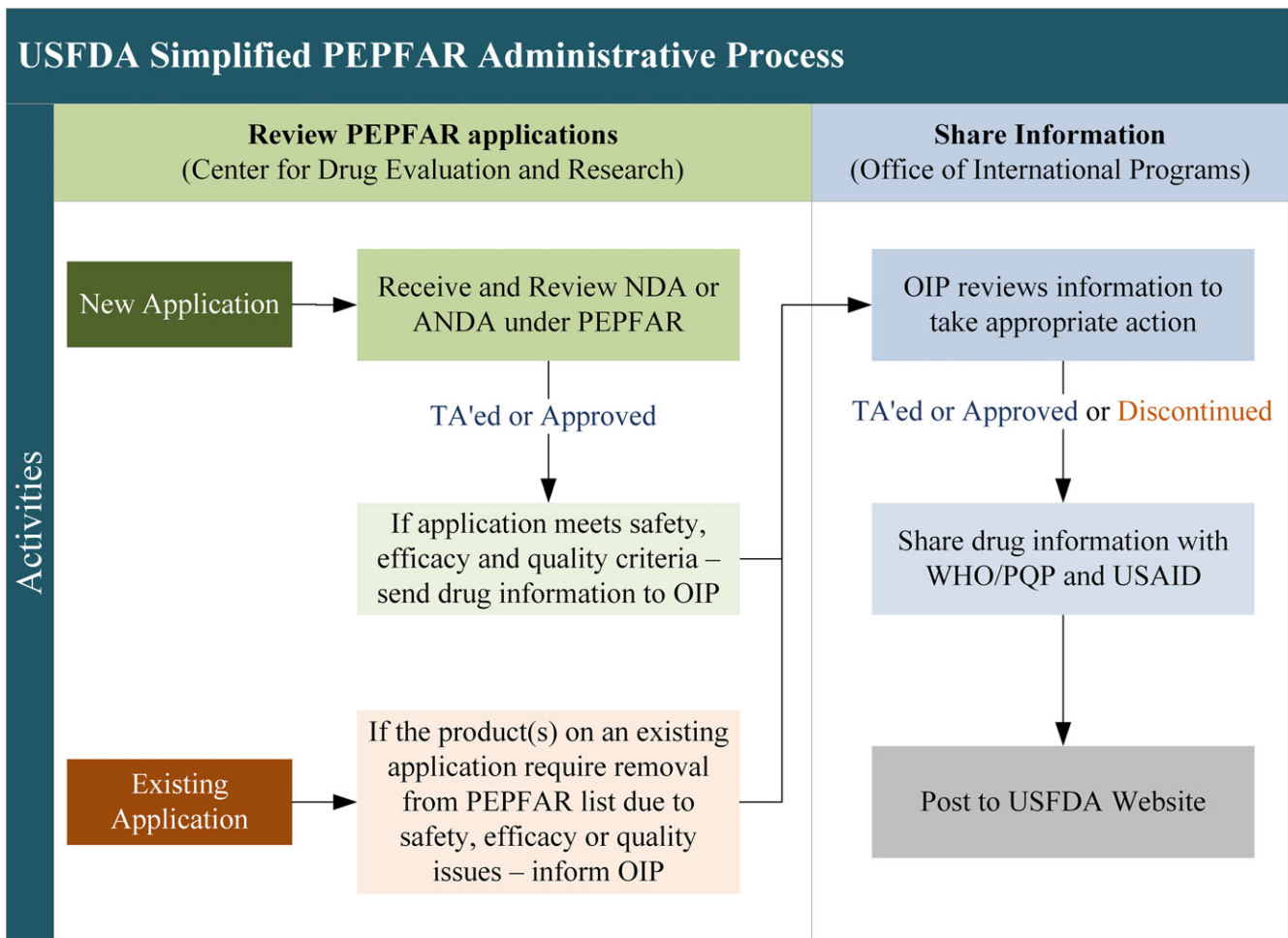


Figure 3. The simplified administrative process of drug review and dissemination of information related to drugs for the PEPFAR programme. The diagram flows from left to right, representing key distinct functions across two offices at the USFDA; and from top to bottom, displaying the various processes involved in fulfilling each function. USFDA, US Food and Drug Administration; PEPFAR, President's Emergency Plan for AIDS Relief; NDA, New Drug Application; ANDA, Abbreviated New Drug Application; TA, Tentative Approval; OIP, Office of International Programs; WHO, World Health Organization; PQP, Prequalification of Medicines Programme; USAID, US Agency for International Development.

States, patents and exclusivities can also affect which products can be submitted and registered with the USFDA under the PEPFAR designation. Patents are granted by the United States Patent and Trademark Office anywhere along the development lifecycle of a drug and can encompass a wide range of claims [27]. They are listed in a publication commonly known as the Orange Book, an online compendium that lists all patents and exclusivities for USFDA-approved drugs; patents can expire or be issued either before or after drug approval [27]. Exclusivity, granted by the USFDA, is an exclusive marketing right given upon approval of an NDA and can run concurrently with a patent [27]. Exclusivity can also be granted to an NDA supplement when the clinical data submitted by the applicant meet the criteria for exclusivity. USFDA-granted exclusivities are not added to the patent life, with the exception of paediatric exclusivity, for which a six-month exclusivity that attaches at the end of all existing marketing exclusivities and patent periods. Paediatric exclusivity is awarded to NDA holders that conduct requested studies in paediatric patients [27,28].

Patents and exclusivities may affect when an applicant can submit an application for review and when an application can be fully approved for marketing in the US [7,27,29]. Specifically, the type and duration of exclusivities granted to NDAs (original innovator applications) can delay the submission of a 505(b)(2) or 505(j) application to the USFDA [7,29]. Table 2 lists the various exclusivities administered by USFDA [27,30].

The exclusivity that impacts when a tFDA application can be submitted is the New Chemical Entity (NCE) exclusivity which grants the holder five years of exclusive marketing rights in the US, starting from the date of NDA approval [7]. In certain circumstances the five-year exclusivity may be reduced to four years when the generic applicant challenges a patent [31]. However, applications for the PEPFAR programme do not usually involve patent challenges, and thus we refer to this exclusivity as lasting five years in this paper. While other forms of exclusivity can also preclude approval or delay the marketing of tentatively approved products in the United States, only the NCE exclusivity prevents an applicant from submitting or USFDA from accepting a 505(b)(2) pathway NDA or an ANDA for TA review [7,30]. For example, as illustrated in the **case study**, the new drug tenofovir alafenamide fumarate (TAF) was approved by the USFDA less than five years ago (in November 2015), and consequently another applicant may not use 505(b)(2) or 505(j) pathways to submit an application containing TAF until November 2020, unless they have the permission of the TAF owner.

Patents, which typically expire 20 years after the date of filing, have less impact on the *submission* of an application for TA and do not limit PEPFAR's ability to purchase and use tFDA ARVs [27].

Alternatively, a PEPFAR applicant may submit an application at any time, if the applicant has permission from the owner of the original 505(b)(1) NDA to use the application data (or if the 505(b)(1) NDA holder waives the exclusivity) [7,30].

2.3.2 | Medicines patent pool (MPP) and the tFDA process

MPP was established in 2010 by UNITAID, a Switzerland-based non-profit, to increase global access to life-saving medicines through collective management of drug-related

patents, which allows innovator and generic manufacturers to share certain intellectual property rights [32]. The overall intent is to encourage drug patent holders to voluntarily allow generic drug manufacturers to produce and sell drugs in selected countries without raising intellectual property concerns [32,33]. The MPP agreements, however, do not impact the laws regulating USFDA's ability to accept applications for PEPFAR use. Even for drug patents in the MPP, the PEPFAR applicants must either wait until the five-year new chemical exclusivity expires or request a waiver from the exclusivity holder. A drug patent holder's participation in the MPP does not constitute a waiver of exclusivity or other intellectual property rights in the US.

2.4 | How are tFDA applications for use by PEPFAR processed at USFDA?

Finally, in Figure 3 we provide a simplified overview of how tFDA applications used by the PEPFAR programme are processed at the USFDA, starting with application review. The overall technical process for tFDA is handled by two USFDA offices – the Center for Drug Evaluation and Research (CDER) and Office of International Programs (OIP). CDER's Office of Generic Drugs and Office of New Drugs are responsible for receiving and reviewing applications for HIV drugs, including for the PEPFAR programme (first column of the figure). Once CDER completes a review and tentatively or fully approves a drug, the information for the drug is sent to OIP for dissemination to the WHO PQP, to the USAID and to the general public via the OIP website (second column of the figure). The same process is followed for removal of existing drugs from the USFDA's quality-assured pool due to safety, efficacy or quality concerns.

3 | CONCLUSIONS

In this paper, we have described the importance of tFDA and how the tFDA is applied to review of ARVs by the USFDA in the context of the PEPFAR programme. We have also discussed the impact of patents and exclusivities on review of HIV drugs under the tFDA. Overall, tFDA has been very successful in making a large number of ARV products available to global programmes to aid the global fight against HIV.

Case study: Tenofovir alafenamide fumarate (TAF)

This case study is intended to highlight how exclusivities and regulatory pathways may interact in the context of PEPFAR for TA using the example of tenofovir alafenamide fumarate (TAF), an HIV drug that was first approved in the US in 2015.

Product description TAF is a new prodrug (a medicine that is converted to its active form inside the body) of tenofovir; a previously approved prodrug was tenofovir disoproxil fumarate (TDF) [34]. TAF and TDF are converted to the same active form inside the HIV-infected cells, but compared to TDF, TAF requires a 90% lower dose for similar anti-viral effect and may have a lower risk of bone and kidney adverse reactions [35–38]. TAF was first approved as part of a four-drug combination for HIV called Genvoya (Cobicistat + Elvitegravir + Emtricitabine + TAF) in November 2015. It was subsequently

combined with other HIV medicines and approved as Odefsey (Emtricitabine + Rilpivirine hydrochloride + TAF) and Descovy (Emtricitabine + TAF) in 2016.

Exclusivities on TAF TAF was recognized as a new chemical entity and thus received a 5-year marketing exclusivity, set to expire on 5 November 2020 [8].

Patents on TAF TAF, as a part of approved combination ARV products, has various patents on it, currently expiring in August 2032 [8].

Regulatory pathways Despite these exclusivities and patents, there are two regulatory pathways for TAF to be registered under tentative USFDA approval for use through PEPFAR funds. First, applicants may use the 505(b)(2) new drug application pathway to create a new drug combination or formulation with TAF, supported by safety and efficacy profiles. In the second pathway, applicants may use the 505(j) or abbreviated new drug application pathway for a generic version of any of the three TAF-containing products already approved by the USFDA.

Timing of submission Given the existing five-year NCE exclusivity, the timing of submission of a TAF-containing regimen application for PEPFAR depends on whether or not the PEPFAR applicants have the permission of the NDA holder. If a waiver to the NCE is obtained, then either an ANDA (505(j)) or an NDA (505(b)(2)) for TA may be submitted at any time by PEPFAR applicants. If such a waiver is not available, then PEPFAR applicants must wait until NCE expiration, regardless of which pathway is followed.

Timeline for review and fees Timeline and fees for the review will depend on whether the application is an NDA or an ANDA. An ANDA will automatically receive priority review and the applicant must pay the current application and other relevant fees (such as drug master file review fee and/or a facility fee). For an NDA, application fees can be waived and determination of priority or standard review will be made upon receipt of application and if requested by the applicant.

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COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHORS' CONTRIBUTIONS

All authors have read and approved the final manuscript. HSC conceived the work, wrote the initial draft, coordinated co-author reviews and revisions. JM, MS, RP, and PC provided in-depth reviews of technical, legal and regulatory content and edited the manuscript multiple times. MLV reviewed, edited and provided feedback on the manuscript. PL provided overall direction and reviewed and substantially edited the manuscript for content and organization.

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