Nineteen Years of PEPFAR

CAPT Monica Zeballos, Pharm.D., R.Ph.
Senior Program Consultant
Division of Antivirals | OID | OND | CDER | FDA

Regulatory Best Practices for Global Access to Medicines, Including Anti-TB Medicines

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Overview

- Regulatory History and Considerations
- PEPFAR From the FDA Point of View
- Change Amendments After Tentative Approval
- Requirements for Final Approval
- FDA PEPFAR Database
- Pre-submission Guidance for NDAs

Regulatory History and Considerations

- S/GAC (formerly OGAC)/PEPFAR policy:
  - Procurement of drugs must be approved by a "stringent regulatory authority" i.e., FDA
- For antiretroviral drugs, only those approved/tentatively approved by FDA are eligible for procurement under PEPFAR as described in the 2006 FDC guidance*

**Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV*
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079742.pdf

Considerations (cont.) Review Timelines for Original Applications

Application Type	Review Determination/Classification	FDA Review Timelines
ANDAs	Prioritization Review[a] is outlined CDER's MAPP 5240.3 Rev. 5	Set by GDUFA II Commitment Letter https://www.fda.gov/media/101052/download
NDAs	Standard	10 months
	Priority	6 months

a = Applications will appear as priority review in a reviewer's work queue

PEPFAR From the FDA Point of View How Does PEPFAR Differ?

- Most applications are Tentatively Approved
- Tentative Approval – Drugs passed all scientific requirements for safety, efficacy, and quality standards, but cannot be marketed in the U.S. due to patents/exclusivities restrictions
  - Not a new regulation. Common practice in the Office of Generic Drugs since 1984
  - All aspects of review and inspections (i.e., manufacturing and BE) must be completed and found acceptable prior to tentative approval
  - However, sale and distribution of Tentatively Approved products (outside U.S.) is unique to PEPFAR

Two Review Paths- Generic (ANDA) vs. New Drug (NDA)

Application Type	General Characteristics	Classification
ANDAs	1. Office of Generic Drugs is lead 2. No Fast Track designation 3. Strict criteria for A or TA 4. No User Fee Waivers prior or after GDUFA	**505(j)** -Has a reference listed drug (RLD) and it relies on FDA's findings of safety and effectiveness for a previously approved drug -Bioequivalent to RLD & in vivo BE studies are required -Same labeling as the RLD -Eligible for A and TA -Generally new animal and clinical data are not needed
NDAs	1. Division of Antivirals in OND is lead 2. Pre-submissions via Rolling Review for Fast Track designed products 3. More flexibility, allows for use of additional clinical info and has different label 4. User Fee Waivers	**505(b)(1)** -Owns/has right of reference for all the investigations needed to support approval -Eligible for A only -Eligible for U.S. legal market protection
		505(b)(2) -Does not own/have right of reference for all the investigations needed to support A or TA -Change from the listed drug -Relies on FDA's previous findings of safety & effectiveness -Relies on scientific literature references for new formulations -Eligible for A or TA -Fasted BE studies are required

Change Amendments After TA Administrative

- **The scientific principles for evaluation remain the same**
- Generally labeling and manufacturing changes only
- To make a risk assessment and determine the type of change
  - Use 2004 Guidance for Industry *Changes to an Approved NDA or ANDA* as well as Q&A document
  - Official cover letter should state type of change
  - Official cover letter should provide a summary of **all** the changes and a justification for choosing the type of change

Change Amendments After TA (cont'd)

- To determine what information or data should be submitted **to support** the proposed change
  - Use the 1995 Guidance for Industry *SUPAC-IR: Immediate Release Solid Oral Dosage Forms*
  - Use the 1998 Guidance for Industry *PAC-ATLS: Post-approval Changes – Analytical Testing Laboratory Sites*
- Annual Update is recommended
  - Stability and distribution data
  - Cumulative list of all the changes amendments

Changes Amendments After TA (cont'd)

Types of PEPFAR Change Amendments and Review Timelines for NDAs

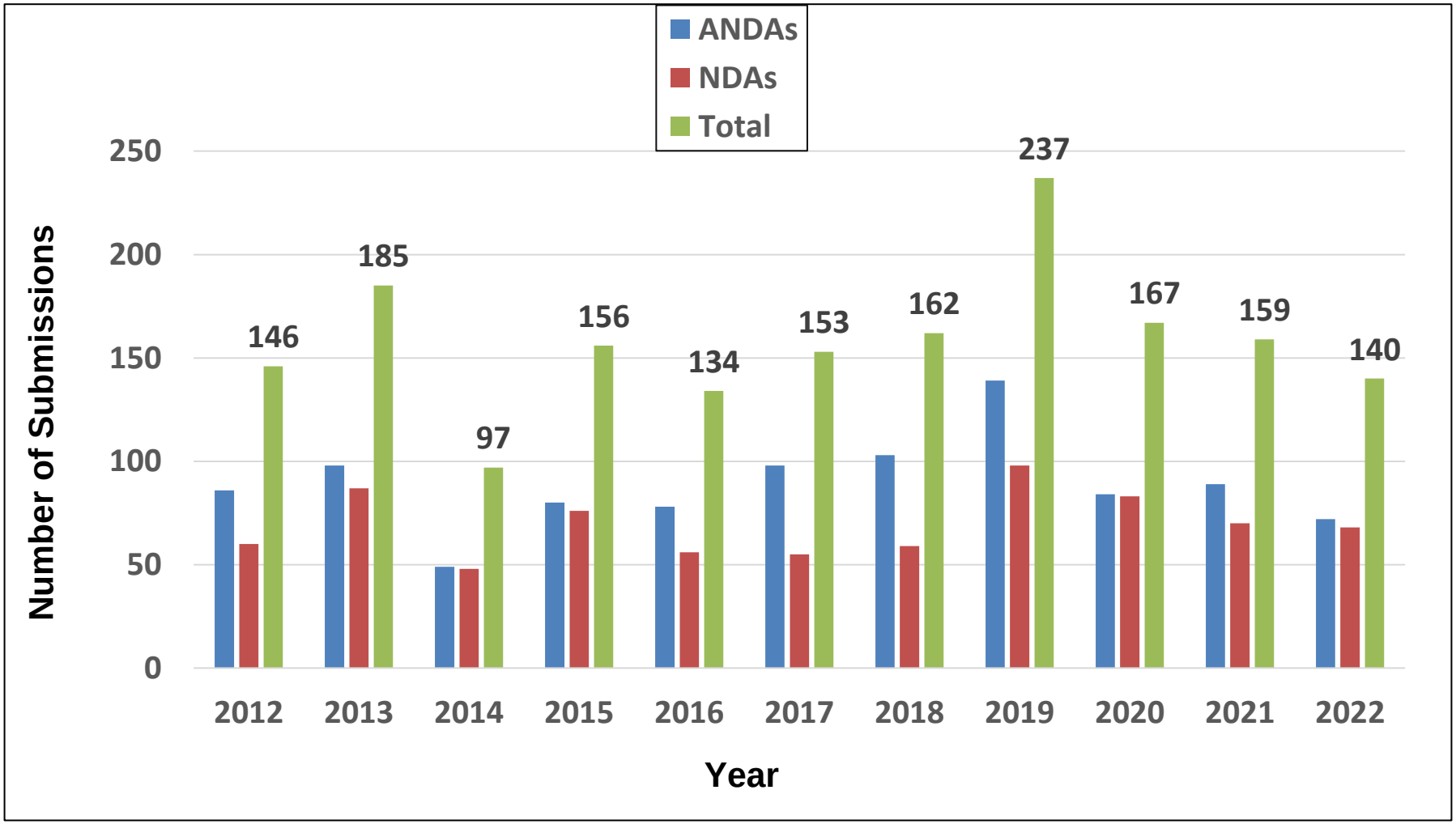
Type of Change	Tentatively Approved NDAs	FDA Review Timelines	Change Amendment Implementation	FDA Decisional Action
Major	Amendment – Major Change	4 months	Requires submission of change and decisional action by FDA before implementation	If change is found acceptable, FDA sends a PEPFAR Permitted letter by the 4-month review timeline
Moderate	Amendment – Moderate Change	6 months	Requires submission of change, but the change can be implemented 30 days after FDA officially receives the submission	If change is found acceptable, FDA sends a PEPFAR Permitted letter by the 6-month review timeline
Minor[a]	Amendment – Minor Change	6 months		

[a] Includes changes that, for approved applications, would be submitted in annual report per 21 CFR 314.70(d

Changes Amendments After TA (cont'd)

- FDA decisional letters
  - PEPFAR Permitted Letter- If change is found acceptable
  - PEPFAR Denied Letter – If change is found unacceptable
  - Original application will remain tentatively approved in either case

Change Amendments Workload 2012-2022



Grand Total 2006 -2022 = 2,194 (1,271 ANDAs and 923 NDAs)

Requirements for Final Approval

- Submit official request for final approval
- Submit the final printed labeling (FPL)
  - Compliant with 21CFR206 (uniqueness of drug product appearance)
  - Submit package insert in Structured Product Labeling (SPL)
- Child-Resistant Packaging Complaint
  - Poison Prevention Packaging Act (16CFR1700)
  - Immediate container, carton, and unit-of-use packing
- For ANDAs, see Sept 2020 guidance *ANDA Submissions — Amendments and Requests for Final Approval to Tentatively Approved ANDAs*

FDA PEPFAR Database Overview

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=pepfar.page

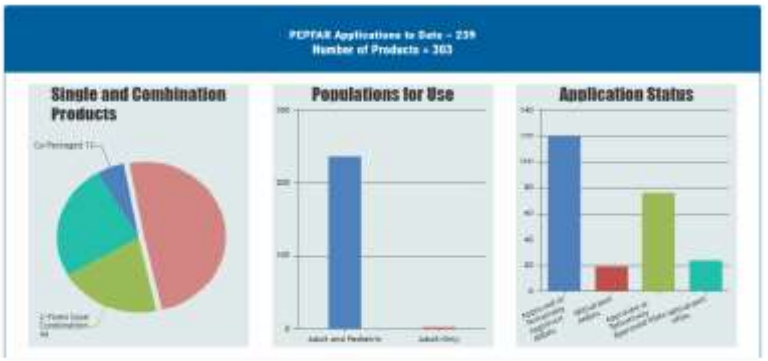
Previous Static Website

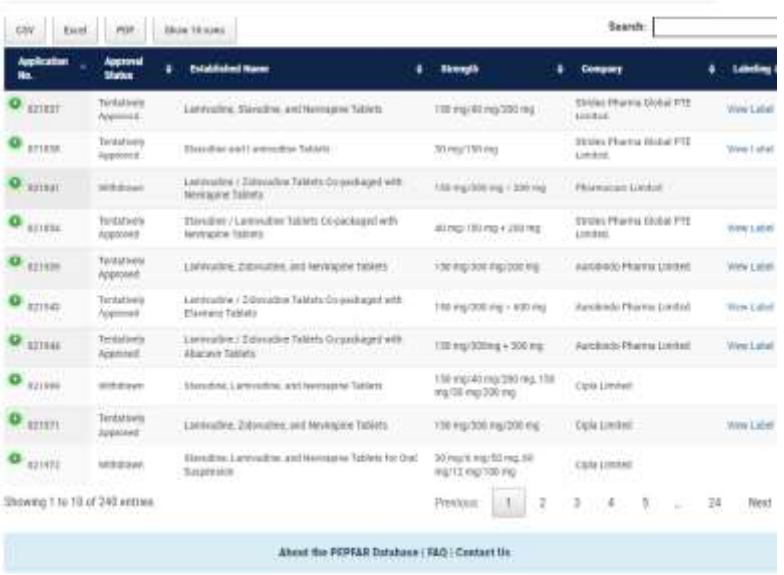
FDA Antiretrovirals Approved and Tentatively Approved in Association with the President's Emergency Plan Expedited Review Process

« Return to Presidential Emergency Plan for AIDS Relief (PEPFAR)

#	Application Number	Established Name	Strength	Dosage Form	Supplier	Manufacturing Site Drug Product	Packaging Material and Pack	Date of FDA Approval or Tentative Approval
211	NDA 210540	Lopinavir and Ritonavir	40 mg / 10 mg	Oral Granules	Mylan Laboratories Limited	Mylan Laboratories Limited (FDF-1) Plot # F/4 & F/12, Malegaon MIDC Sinnar, Nashik District- 422113 Maharashtra India	Cartons containing 120 aluminum foil sachets	Tentative Approval 8/16/2018
210	NDA 205626	Lamivudine, Nevirapine and Zidovudine	150 mg / 200 mg / 300 mg	Tablets	Micro Labs Limited	Micro Labs Limited Plot No. S-155 to S-159 & N1, Phase III & Phase IV Verna Industrial Estate, Verna, Goa – 403722 India	HDPE bottles containing 60 tablets with induction seal and child-resistant cap	Approved 8/13/2018
209	NDA 210680	Dolutegravir, Lamivudine, and Tenofovir Disoproxil Fumarate	50 mg / 300 mg / 300 mg	Tablets	Hetero Labs Limited	Hetero Labs Limited, Unit III Plot No. 22-110, Part-II, Industrial Development Area Jeedimetla, Hyderabad, Telangana, 500055 India	HDPE bottles containing 30, 60, 90, 100, or 750 tablets with desiccant, induction seal and child-resistant closure	Tentative Approval 8/8/2018
208	ANDA 209602	Dolutegravir	50 mg	Tablets	Mylan Laboratories Limited	Mylan Laboratories Limited Plot No. 11, 12 & 13, Indore Special Economic Zone, Pharma Zone, Phase – II, Sector – III, Pithampur District Dhar, Madhya Pradesh India	HDPE bottle packs of 30 with non-child-resistant closure	Tentative Approval 7/6/2018

Database Launched Jan 2020





FDA PEPFAR Database (cont'd)

- Interactive, searchable, mobile-friendly database provides real-time insight into key metrics and for the first time, access to FDA-reviewed product labeling
  - Original drug applications – 239 TA/A
  - Change amendments permitted
- Enhances communications with internal/external stakeholders to increase transparency
- Provides greater utility and access to stakeholders seeking drug product labeling, pediatric uses, shelf-life, and other critical information on ARVs eligible for procurement under PEPFAR

Pre-Submission Guidance for NDAs

- To obtain pre-submission guidance for original NDAs, use the Division of Antivirals Pre-IND Consultation Program

  http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/ucm077776.htm

  - This program is useful to discuss specific product quality questions (e.g., listed drug, dissolution method (including profile and acceptance criterion), morphic form stabilization).
  - You don't need a "real" IND! Program is applicable to pre-NDA and pre-DMF discussions.
  - We can have a teleconference or provide written responses only.

Thank You!

Presentation Questions?