Regulatory Approval Process for Generic Antiretroviral Drug Products

Xiaofei Wang, Ph.D.

Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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The PEPFAR Program

- The US government initiative (2003) to help save the lives of those suffering from HIV/AIDS throughout the world
- The cornerstone and the largest component of the US president's Global Health initiative

FDA's Role Under PEPFAR

- Improve the drug regulatory environment
- Ensure the availability of safe, effective and affordable antiretroviral drugs (ARVs)
- Provide a comprehensive regulatory review of applications for marketing ARVs under PEPFAR
  - FDA's Office of New Drugs evaluates applications for new fixed-dose combination (FTC) and co-packaged ARVs
  - FDA's Office of Generic Drugs (OGD) evaluates applications for generic versions of ARVs

A Unique Drug Approval Process for Generic ARVs

- OGD grants “full approvals” for FDC, co-packaged, or generic ARV not under US patent/exclusivity protection
  - Can distribute in PEPFAR countries and market in US
- OGD grants “tentative approvals” for FDC, co-packaged, or generic ARV still under US patent/exclusivity protection
  - Can distribute in PEPFAR countries (with licensing agreement from innovator) but not market in US
- Only fully or tentatively approved FDC, co-packaged, or generic ARVs can be purchased and distributed in PEPFAR countries

PEPFAR ANDA Review by OGD Divisions

DIVISION	Labeling & Program Support	Chemistry	Bioequivalence
REVIEW ACTIVITIES	Ensures that ANDA is substantially complete before assigning for review	Reviews CMC data	Reviews in vivo BE and in vitro dissolution data; First-in, first-reviewed policy
PEPFAR PROCESSES	Will accept ANDAs with some pending deficiencies & allow "rolling review"	Pre-review of DMF; Pre-inspection of manufacturing facilities	Initiates review upon receipt; Pre-inspection of clinical & analytical facilities

A Unique Drug Approval Process for Generic ARVs

- OGD performs all reviews of PEPFAR applications on an expedited/priority basis
  - Very short review time goals (2-6 weeks)
  - Pre-assigned ANDA numbers
  - High level of oversight throughout review process
  - Close collaboration with firms to facilitate complete review within one cycle (< 6 months)
  - Staff expedite inspections of clinical, bioanalytical sites before approval

OGD Places the Same Standards for Generic ARVs

- Standards applied to PEPFAR drugs are the same as for drugs approved for US marketing
- Drugs approved under PEPFAR meet all of FDA's manufacturing quality, clinical safety, efficacy requirements

Characterizing BE in PEPFAR ANDAs

- Bioequivalence

  the 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 (21CFR §320.1)

Characterizing Bioequivalence (BE) in PEPFAR ANDAs

Reference product for BE studies

Must be a drug product approved in US

Batch used in BE studies

At least 100,000 dosage units	Or 10% of final batch size, whichever is larger

Appropriate design for in vivo BE studies in healthy normal subjects

Randomized, single-dose crossover or parallel	Usually a fasting BE study & a fed BE study

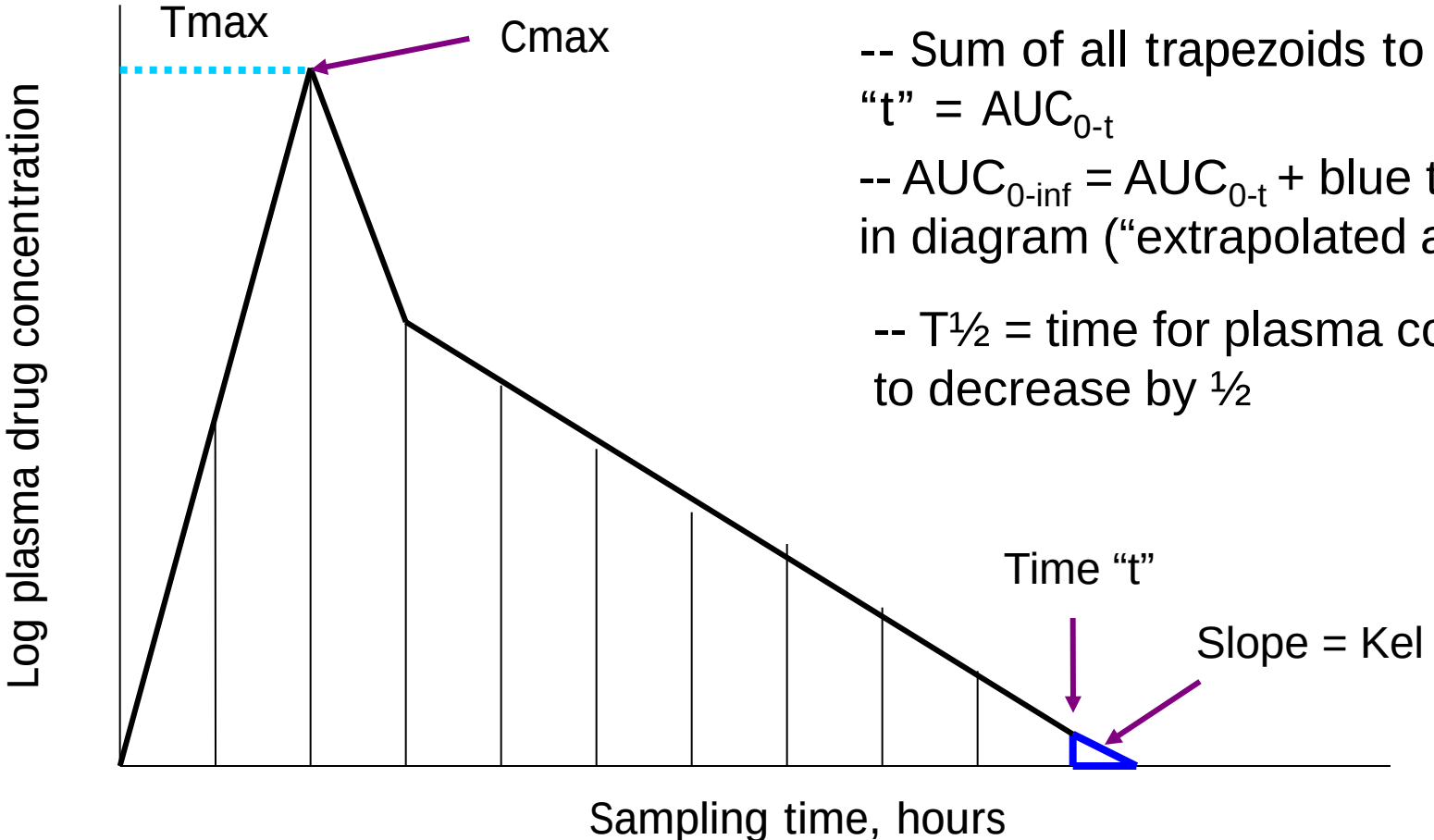
Characterizing BE in PEPFAR ANDAs

- Bioanalytical Method: well-characterized, fully-validated, and documented

- Pre-study Bioanalytical Method Validation should determine the following
  - Assay selectivity
  - Assay precision and accuracy
  - Stability of stored analyte(s) (i.e. drug and metabolite, if applicable) in various matrices
  - Recovery of analyte(s) and internal standard
  - Assay limit of quantitation (LOQ)

Characterizing BE in PEPFAR ANDAs

- Pharmacokinetic Parameters
  - Peak plasma concentrations (Cmax): rate of absorption
  - Area under drug concentration vs. time profile (AUC): extent of absorption



-- Sum of all trapezoids to Time "t" = $AUC_{0\text{-}t}$

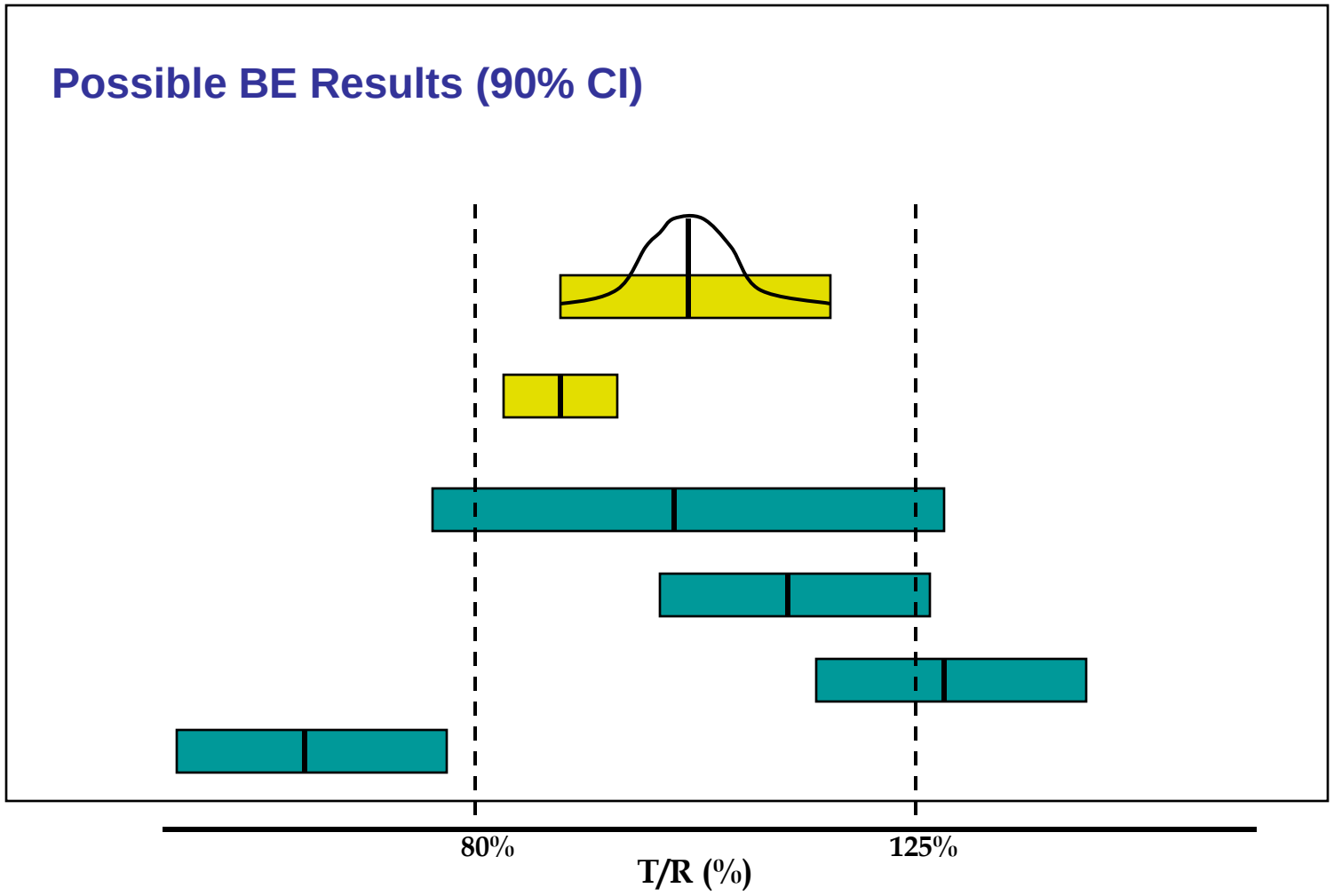
-- $AUC_{0\text{-}inf}$ = $AUC_{0\text{-}t}$ + blue triangle in diagram ("extrapolated area")

-- T½ = time for plasma conc to decrease by ½

Characterizing BE in PEPFAR ANDAs

- Statistics: Use ANOVA with two one-sided tests procedure to statistically analyze BE study data (*Schuirmann DJ, J Pharmacokinet Biopharm. 1987 Dec;15(6):657-80*)
- BE criteria are that the 90% confidence intervals of geometric mean AUC_{0-t} , AUC_{∞} and C_{max} Test/Reference ratios must fall within 0.800 to 1.250
  - Rounding up or down is not permitted
- T_{max} may also be evaluated, if rapid onset of effect is necessary for efficacy
- Dissolution: Evaluate if a discriminating dissolution method is developed, with limits set, for each active pharmaceutical ingredient (API) in the drug product

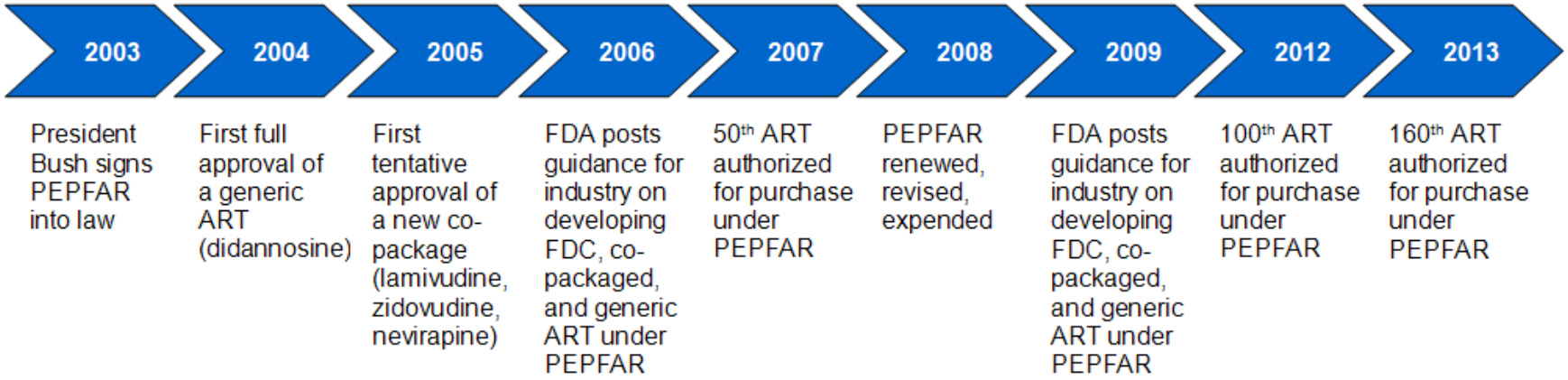
Characterizing BE in PEPFAR ANDAs



PEPFAR Post-Approval Activities

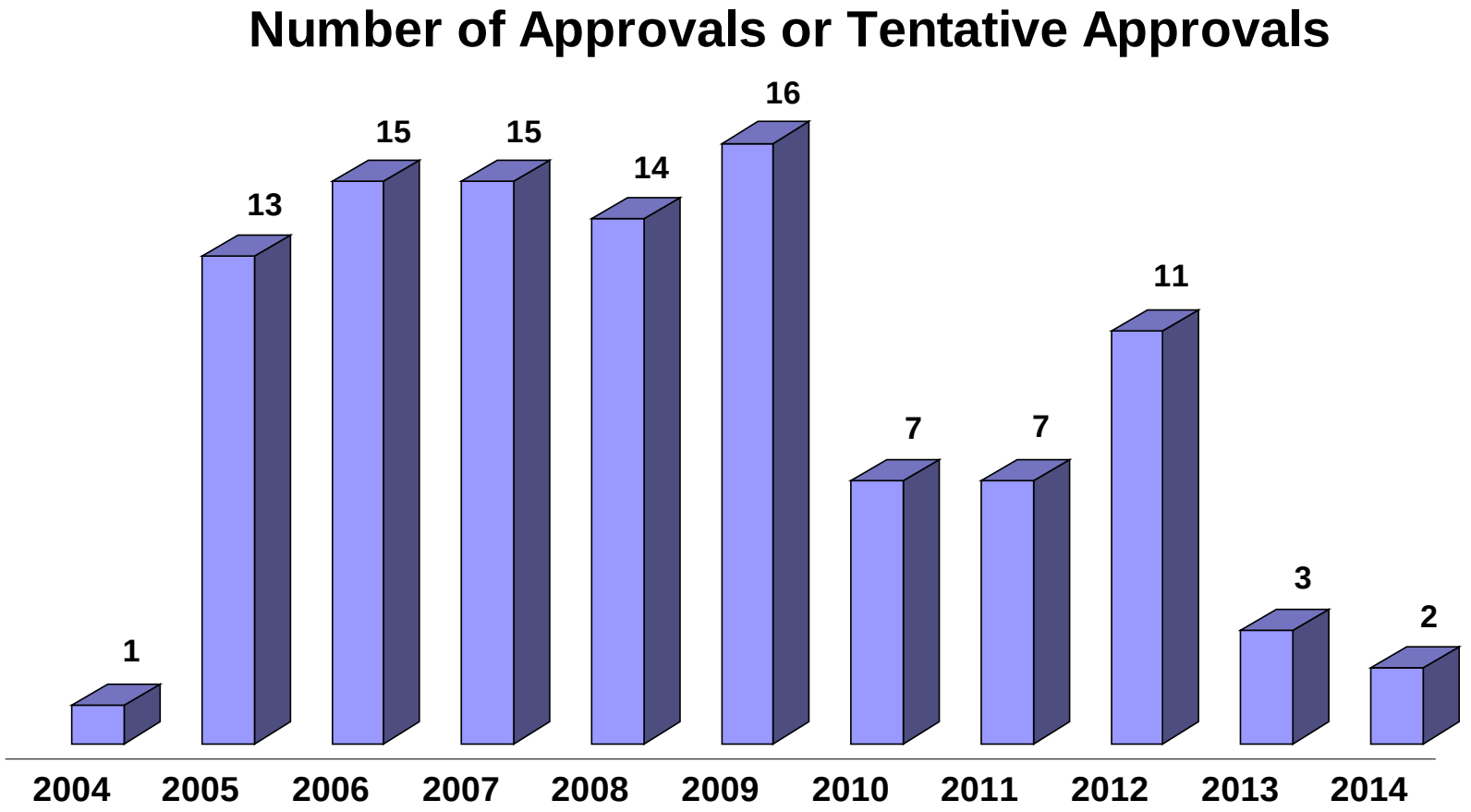
- FDA monitors the approved drug products by reviewing adverse event reports, to ensure continued drug safety after products enter the market
- FDA reviews any changes made to the approved products to ensure that the products continue to be safe, effective, and of acceptable manufacturing quality

FDA's PEPFAR Implementation Timeline



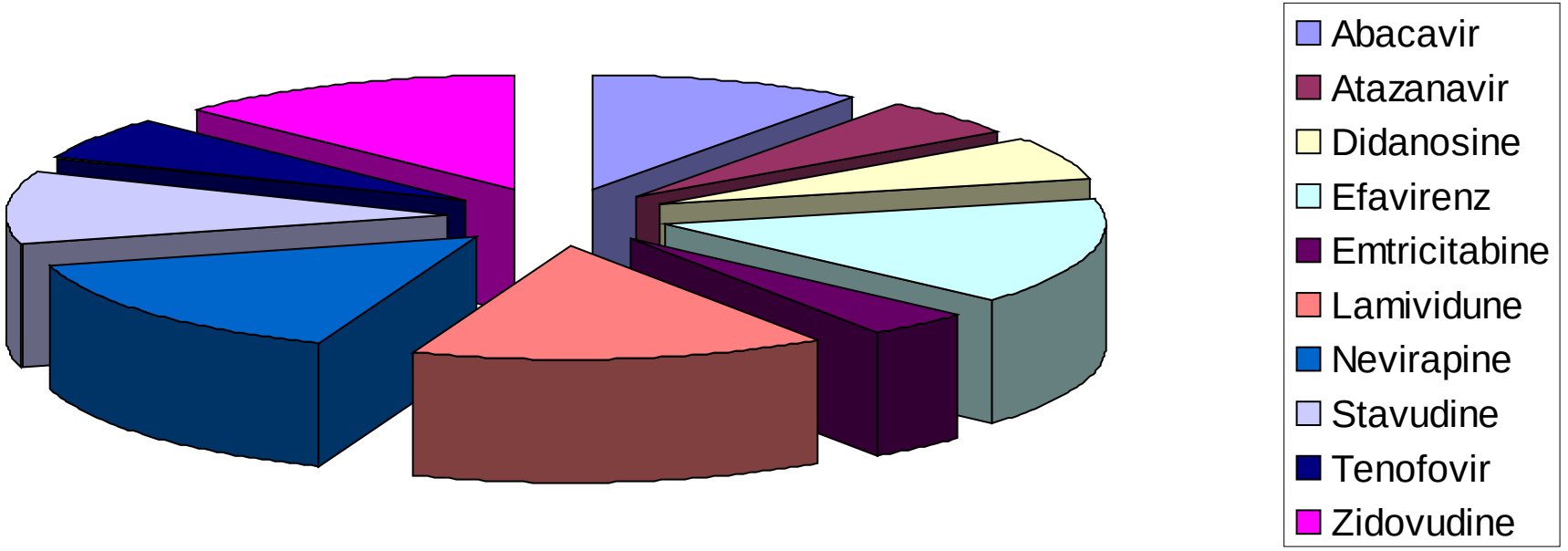
- As of this writing, 168 drug products are approved or tentatively approved under PEPFAR
  - 104 generics
  - 64 new FTC or co-packaged products

Generic PEPFAR Approvals per Year



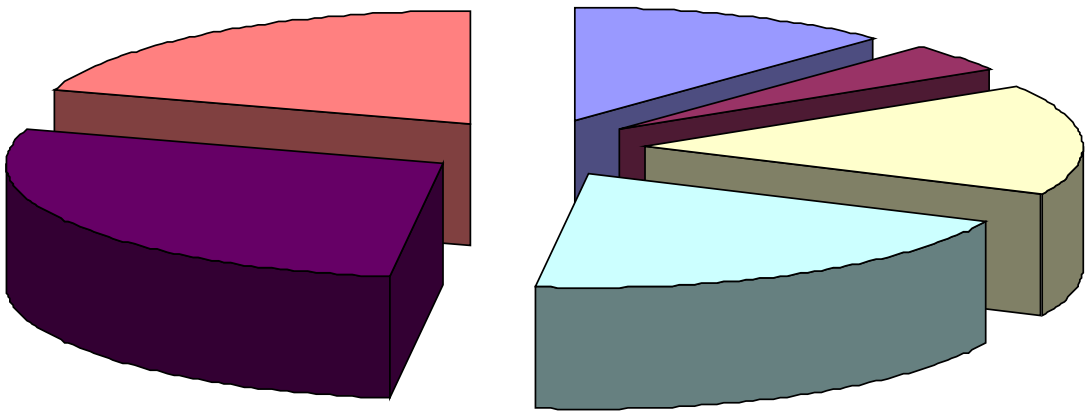
Available Generic PEPFAR Drugs

Generic antiretroviral monotherapy products approved or tenratively approved to date (N=79)



Available Generic PEPFAR Drugs

Generic antiretroviral combination therapy products approved or tentatively approved to date (N=25)



- Abacavir + Lamivudine
- Abacavir + Lamivudine + Zidovudine
- Efavirenz + Emtricitabine + Tenofovir
- Emtricitabine + Tenofovir
- Lamivudine + Zidovudine
- Lopinavir + Ritonavir

Summary and Conclusions

- The US PEPFAR initiative has saved lives of those suffering from HIV/AIDS
- FDA ensures the availability of safe, effective and affordable antiretroviral drugs (ARVs)
- FDA's OGD developed an expedited process for reviewing potential generic products to be distributed under PEPFAR
- FDA's OGD uses the same stringent criteria in the review of generic ARVs applications
- To date, 104 generic antiretroviral drug products are approved or tentatively approved for distribution in PEPFAR countries

References

- The United States President's Emergency Plan for AIDS Relief, http://www.pepfar.gov
- USAID, http://www.usaid.gov
- US-DHHS Global Health, http://www.globalhealth.gov
- US-FDA, http://www.fda.gov

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Thank you for your attention!