

Regulatory Issues Related to Fixed Dose Combination Drugs for the Treatment of HIV Infection— FDA Perspective

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Note: Opinions stated in this presentation are those of the presenter and do not indicate FDA policy

Outline

- Components of an FDC NDA
- Significant Regulatory and Scientific Issues
- Pediatric Issues
- Related Issue
 - Introduction of non-US approved drug products in clinical trials

FDC Guidance...

- Draft Guidance for Industry: Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV
 - Provides guidelines for rapid approval of innovator or tentative approval of non-innovator drugs for distribution outside the U.S.
 - Intended to support PEPFAR purchase of ARV drugs

Definitions

- Fixed dose combination - a single product containing two or more drug ingredients; both components contribute to product's effectiveness
- Co-packaged products - two or more products in their final dosage form packaged together for ease of use or distribution

Guidance: What Products?

- Combinations of ARV drugs (individual drugs have FDA approval)
 - FDCs
 - Co-packaged products
- Approach may apply to individual drugs (through Office of Generic Drugs)
- Innovator (brand)
- Non-innovator (non-brand)
- Processes are the same; amount of information depends on the product type

Components of an FDC NDA

- Clinical rationale for combination
- Clinical Pharmacology and Biopharmaceutics
- Chemistry, Manufacturing, and Controls (CMC)

Clinical Components

- Summary or rationale for clinical use
- Reference previous IND/NDA (innovator)
- Right of reference to other sponsor's IND/NDA
- Literature References
 - Clinical studies: 48-wk effect on HIV-RNA
 - Other data: resistance studies, safety data
 - Treatment guidelines (WHO, DHHS, IAS)
- Rely on FDA's previous findings of safety and effectiveness

Clinical Pharmacology and Biopharmaceutics Components

- Bioequivalence study (studies)
- Bioanalytical method validation
- Summary of food effect considerations
- Dissolution testing

Chemistry/Manufacturing Components

- Quality standards for each active ingredient and dosage form
- Stress studies: lack of interaction between ingredients
- Drug release information (dissolution)
- Stability data: long term and short term under high temperature and/or humidity
- References/data supporting excipients
- Manufacturing processes for active ingredients and dosage form

Significant regulatory and scientific issues with FDCs and co-packaged drugs for HIV

- Selection of appropriate drug combinations
- Type of application (NDA or ANDA)
- Reference formulation (US RLD; non-US ref.)
- Availability of fasted and fed BE data
- General BE study design
- Statistical issues for BE studies
- Short review timeline
- Expedited DSI and compliance inspections

Selection of appropriate drug combinations

- Full (3 drug) or partial (2 drug) regimens
- Preferred/alternate regimens in treatment naïve pts
- Clinical trials of proposed combination (48 wks)
- Favorable risk-benefit profile
- Once or twice daily administration
 - FDC: same schedule for all components
 - Co-pkg: prefer same schedule, but not essential
- Easy administration and compatible dosing schedules and food requirements

Examples of Combinations

2-drug combinations

(use with a 3rd drug)

- *abacavir + lamivudine
- didanosine + lamivudine
- didanosine + emtricitabine
- stavudine + lamivudine
- *tenofovir + emtricitabine
- tenofovir + lamivudine
- *zidovudine + lamivudine

3-drug combinations

- abacavir + lamivudine + lopinavir/ritonavir
- abacavir + lamivudine + nevirapine
- abacavir + lamivudine + efavirenz
- didanosine + emtricitabine + efavirenz
- stavudine + lamivudine + efavirenz
- stavudine + lamivudine + lopinavir/ritonavir
- stavudine + lamivudine + nelfinavir
- stavudine + lamivudine + nevirapine
- tenofovir + emtricitabine + efavirenz
- tenofovir + lamivudine + efavirenz
- *zidovudine + lamivudine + abacavir
- zidovudine + lamivudine + efavirenz

From Appendix B of FDC Guidance

*available as FDC product in US

Type of Application (NDA or ANDA)

- New FDC products and new co-packaged combinations must be submitted as NDAs.
- Products with approved US reference (FDC or single entity product) are submitted as ANDAs.

Selection of appropriate reference formulations for FDCs & co-packaged drugs

- Some sponsors conducted BE studies using European or other foreign approved products as the reference products. To conserve resources and bring the products to market as soon as possible, the sponsors do not want to repeat the BE studies.

Selection of appropriate reference formulations for FDCs & co-packaged drugs

- **ANDA-** proposed product (test) must be compared to the US approved reference listed drug (RLD)
- **NDA [505(b)(2)]-**
 - Consider similarity of US RLD and the approved foreign product (from the same company as US product)
 - Some US sponsors are willing to provide a limited right of reference to comparative information between their US and foreign products (PEPFAR program, only)

Availability of Fasted and Fed BE data

- Some sponsors conducted BE studies under fasted conditions only. If they need to conduct a fed BE study prior to submission, it will delay the application.

Availability of Fasted and Fed BE data

- **ANDA**

- In addition to a fasted BE study, OGD recommends that fed BE studies be conducted for all oral drugs
- Exceptions
 - Drug is BCS Class I
 - RLD label states the drug should be taken on an empty stomach
 - RLD label does not make statements about the effect of food.
- HIV FDC products need a fed BE assessment, unless the components include didanosine or efavirenz.

Availability of Fasted and Fed BE data

- **NDA [505(b)(2)]**
 - DAVDP will accept applications for FDC or co-packaged products without a fed BE study or a food effect study.
 - The label for such products will indicate that the effect of food is not known and the product should be taken under fasted conditions.

Other Issues

- General BE study design
- Statistical issues for BE studies
 - Need to meet 80-125% for AUC and Cmax*
- Short review timeline
- Need for expedited DSI and compliance inspections

Application of pediatric initiatives to FDC development

- Want to encourage development of FDCs appropriate for pediatric patients
- Some FDCs may not be appropriate for all ages
 - dose, proportion of component drugs
- Consider on a case-by-case basis

Approaches to pediatric formulations

- Approved formulations: Liquids predominate; one oral powder
- Must be open to other approaches and extemporaneous formulations
 - Delavirdine - disperse tablet in water; example where bona fide formulation not achieved after sufficient developmental effort

Evaluating pediatric formulations

- Bioequivalence studies can be conducted in adults
- If comparing 2 oral solutions no BE study required, if comparing formulations other than solutions BE study required
- Important considerations
 - Palatability
 - Volume of liquid

Introduction of non-US approved products in clinical trials

- Consider intent of study- are there plans to extrapolate results to other formulations?
- Optimal to compare to reference product prior to use in clinical trial
- Clinical trials - probably difficult to interpret if sponsor uses different products at different sites in same trial

Introduction of non-US approved products in clinical trials

FDA recommendations

- CMC data for product
 - description of drug substance
 - method of preparation
 - components in final drug product
 - stability testing
 - description of packaging
 - limits and analytical methods used to assure quality
- Bioequivalence or relative bioavailability
 - evidence that therapeutic exposure likely to occur

Conclusions

- Our review of applications for products to be procured by PEPFAR program will allow us to have an impact on public health beyond US borders.
- The need to provide drugs that are safe, effective, convenient, and economical requires us to carefully consider **complex scientific and regulatory issues**.
- As we address each issue, we remember that the ultimate goal is the provision of HIV drug products of the **same quality as those provided in the US**. We need to use the allotted money to provide drug products to the largest number of people possible.