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**Developing Fixed-Dose Combination Drug
Products to Treat HIV Disease: The
HHS/UNAIDS/WHO/SADC *Principles Document*
and the FDA *Guidance for Industry***

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Topics Discussed

- ◆ *Scientific and Technical Principles for Fixed Dose Combination Drug Products for the Treatment of HIV/AIDS, Malaria and Tuberculosis (Principles Document)*
- ◆ *FDA Draft Guidance for Industry: Fixed-Dose Combination and Co-Packaged Drug Products for Treatment of HIV (Draft FDA Guidance)*



Principles Document: Intro

- ◆ HIV/AIDS, tuberculosis, malaria are the foremost infectious disease threats facing the world today
- ◆ Combination therapy is considered essential in treating these diseases
- ◆ An important approach is developing fixed-dose combinations (FDC) of drugs
- ◆ A principles document was developed to address development of FDCs



Principles Document: Development

Feb '04: Small group met in South Africa, drafted document

March '04: Document presented at conference in Botswana

Apr '04: Document posted on web, comments accepted

May – Aug '04: Planning group incorporated comments into document

Dec '04: Final version posted at www.globalhealth.gov



Principles Document: Advantages of FDCs

- ◆ Improved adherence
- ◆ Convenience of use
- ◆ Reduced pill burden/simpler treatment regimens
- ◆ Facilitation of logistics of procurement, distribution, dispensing



Principles Document: Purpose

- ◆ Contains guidelines to facilitate and promote development of FDCs
- ◆ Not intended to be a regulatory guideline
- ◆ Applies to both innovator and generic pharmaceutical companies
- ◆ Emphasizes efficacy, safety, quality
- ◆ Describes four possible scenarios



Principles Document: Scenario 1

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|------------------------------|---|
| Scenario | A generic bioequivalent (BE) to existing FDC |
| Microbiology | Not needed |
| Nonclinical pharm/tox | Not needed |
| Clinical | In vivo bioequivalence (BE), compare generic to FDC |



Principles Document: Scenario 2

| | |
|------------------------------|--|
| Scenario | Proposed new FDC, established safety & efficacy of active drug components in combination |
| Microbiology | Not needed |
| Nonclinical pharm/tox | Not needed |
| Clinical | In vivo BE, compare new FDC to drug components given together |



Principles Document: Scenario 3

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|------------------------------|--|
| Scenario | New FDC, safety & efficacy established for individual active components but not combination |
| Microbiology | May be needed to determine the advantage of FDC over individual active components |
| Nonclinical pharm/tox | Case-by-case basis |
| Clinical | <ul style="list-style-type: none">◆ PK or PD drug-drug interaction studies◆ Clinical trials to demonstrate safety/efficacy of new combination or regimen◆ May be acceptable to substitute historical clinical data, PK bridging data |



Principles Document: Scenario 4

| | |
|------------------------------|--|
| Scenario | New FDC comprised of one or more new molecular entities |
| Microbiology | May be needed to determine the advantage of FDC over individual active components |
| Nonclinical pharm/tox | <ul style="list-style-type: none">◆ A complete evaluation◆ Include genotox, reprotox, toxicokinetic studies |
| Clinical | A comprehensive clinical program is needed |



Principles Document: Postlicensing Surveillance

- ◆ Shared responsibility
 - ▶ Physicians, patients, other healthcare providers, manufacturers, regulators
- ◆ Concerns specific to FDCs for HIV/AIDS, malaria, tuberculosis
 - ▶ Adverse events due to one of the components
 - ▶ Additive, synergistic toxicities
 - ▶ Changes in pathogen resistance profiles
 - ▶ Diminishing efficacy



Principles Document: Quality

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|-----------------------|--|
| Drug Substance | Characterize impurities, particle size, polymorphism |
| Drug Product | <ul style="list-style-type: none">◆ Process development◆ Compatibility of individual active components in dosage form◆ Compliance with regulatory or compendial specifications◆ In-process controls |
| Stability | Specific for geographic region |



FDA Draft Guidance: Development

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|--------------------|--|
| Issued in | May 2004 (as draft) |
| Drafted by | Several Offices within FDA/CDER |
| Intended to | Encourage sponsors to submit to FDA applications for marketing approval of new and generic FDCs and co-packaged drug products to treat HIV |



Draft FDA Guidance: Appropriate Combinations

- ◆ Individual components or FDCs must be already approved by FDA
- ◆ Combinations should be supported by adequate evidence of safety, efficacy
- ◆ FDC components should have same dosing frequency and similar food instructions
- ◆ Guidance lists example combinations



Draft FDA Guidance: Submissions to FDA

- ◆ Regulatory procedures
 - ▶ Priority review, fast track
- ◆ Clinical considerations
 - ▶ New clinical trials not needed
 - ▶ Should reference material previously submitted to FDA and peer-reviewed literature
- ◆ Clinical pharmacology/biopharmaceutics
 - ▶ Pivotal clinical studies are BA or BE studies



Draft FDA Guidance: Submissions to FDA

- ◆ Chemistry, manufacturing, controls
 - ▶ Drug substance
 - ▶ Drug product
 - ▶ Stability
 - ▶ Issues unique to FDCs
 - Lack of interaction between active ingredients
- ◆ Microbiology/virology
- ◆ Adverse event reporting



Draft FDA Guidance: Approval Mechanisms

| | |
|------------------|---|
| Full | <ul style="list-style-type: none">◆ Two or more innovators develop a new FDC or co-packaged product◆ Innovator grants license to use drug◆ Patent on drug has expired◆ Firm challenges unexpired patent, and<ul style="list-style-type: none">▶ Innovator doesn't sue; or▶ Innovator sues but court finds patent invalid or not infringed |
| Tentative | <ul style="list-style-type: none">◆ Patent on drug substance still valid◆ Product cannot be marketed in US |



Summary

- ◆ HHS/UNAIDS/WHO/SADC developed a scientific/technical principles document addressing development of FDCs to treat HIV/AIDS, tuberculosis and malaria
- ◆ The FDA provides guidance to industry together with expedited review for FDC and co-packaged drug products to treat HIV/AIDS
- ◆ The goal of these efforts is to impact public health throughout the world



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Thank You