PEPFAR – A US Government Program That is Helping to Keep Millions Alive Around the World

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A Short History of AIDS

- 1981 First reports of previously rare diseases in homosexual patients
- 1983 HIV-1 discovered
- 1987 AZT introduced as first drug
- 1995 Saquinavir first protease inhibitor
- 1996 Nevirapine first NNRTI
- 1996 Combination drug therapy HAART
- 2003 PEPFAR
• A new disease is identified
• The causative agent (HIV) is identified
• The biochemistry of the virus is worked out and possible targets identified
• Drugs that will attack these targets are rationally designed
• Practical formulations are devised
• People who were planning their funerals start to wonder what to do with the rest of their lives
Disease Progression

• HIV destroys CD4 T cells over a period of 8-10 years
• Below a CD4 count of 200 the risk of AIDS-defining illnesses increases
• These are opportunistic infections and certain neoplasms
• Death occurs because of one or more of these illnesses
The Problem (at the beginning of the 21st Century)

- Millions of people are infected
- Most of them live in resource-poor countries in sub-Saharan Africa
- Drugs are very expensive
- Drugs are covered by patents
At least part of the solution

• Drug companies agree not to enforce patents for drugs manufactured for use in resource-poor countries
• Drugs will be manufactured in low-cost countries and applications will be submitted to FDA
• FDA agrees to review these applications to our customary standards
• Large sums of money will be provided
Consider the Challenges

• Atripla, a common treatment, contains:
  – Efavirenz 600 mg
  – Emtricitabine 200 mg
  – Tenofovir disoproxil fumarate 300 mg

• A total 1100 mg of complex, chirally pure synthetic chemicals

• 400 g/year

• For 1 million people = 400 tons/year

• Additionally formulation, packaging, distribution costs (cost of drugs is < 50%)
Complex Structures

Efavirenz

Emtricitabine

Tenofovir Disoproxil Fumarate
U.S. President’s Emergency Plan for AIDS Relief

- Initiated by President Bush & passed in 2003
- Since reauthorized
- US Government funding $52 billion to date
- 6.7 million people on treatment
From the FDA’s Point of View

- Applications are reviewed to FDA’s customary standards (but we do waive the user fees)
- “Approved” if there are no outstanding patent issues
- “Tentatively Approved” (TA) if patent issues would prevent marketing in the US
- Copies of existing products reviewed by the Office of Generic Drugs
- Others reviewed by ONDQA
How the Review Process Works

• The applicant submits (mostly electronically) documents describing every aspect of the manufacturing process
• FDA reviewers read these documents and produce internal reports
• Information requests are sent to the applicant
• Eventually Approval or TA is granted
• Deadlines govern the process
• The review process is resource intensive. We don’t take any short cuts!
• For PEPFAR most of the work is done by chemists and biopharmaceutists in OGD and ONDQA
• PEPFAR products do not contain new molecular entities but they may contain new combinations of existing drugs
• For administrative convenience drug substances are generally described in Drug Master Files (DMFs)
Importantly

• Approved products can be marketed in the US (although the manufacturer may choose not to do so for financial reasons)

• The only reason that Tentatively Approved products cannot be marketed in the US is that there are outstanding patents

• “We would give these drugs to our own people”

• Now 170 Approved or TA’d applications
Communication and the Development of Policy

• Drug development and manufacture is regulated by the Food, Drug and Cosmetic Act, Code of Federal Regulations, and Guidances

• Many of the technical details are covered in the Guidances issued by FDA
For PEPFAR

• Guidance issued in 2006
• “Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV”
• Contains recommendations and procedures to speed the approval process
• Tentative Approval not a novel concept but the application to PEPFAR was new
FDA-PEPFAR Manufacturer Interactions

In all cases the interaction goes both ways

• FDA-Manufacturer interaction during the review of applications

• FDA-Manufacturer interaction through public forums such as the CHAI* supplier meetings – video conference and response to questions

*Clinton Health Action Initiative
Also

• FDA-Distributor interaction through communication with distributor SCMS
• Outreach efforts
  – Participation in conferences
  – Training foreign regulators
• Publications
• Talks
Review Interactions

• Typically (for ONDQA) a new NDA is reviewed and an Information Request (IR) sent to the applicant

• The applicant’s response is reviewed and a second (hopefully shorter) IR may or may not be required

• IRs and responses are in writing (fax and e-mail) and are sent by project managers after supervisory review
• IRs and responses do not touch on general questions.
• Technical issues specific to the application are discussed
• A few years ago we analyzed the questions in the IRs and identified the section of the application to which they referred
  – (Results would probably be different if we did the study today)
For drug products specifications and stability generated the most questions
For drug substances in DMFs the control of starting materials and intermediates was important.
Dissolution Methods

• The performance of drug products (e.g., tablets, capsules) is tested by seeing how rapidly they dissolve under tightly specified conditions. For example, 1 L of 100 mM HCl stirred at 50 rpm at 37°C.

• To make things easier FDA established an on-line database of methods that have been found to be acceptable in 2004

• However, methods are dependent on the exact nature of the formulation so FDA may request changes

• In this case communication with FDA before the NDA is submitted, while there is still time to make changes, can be very helpful
On-Line Information at FDA

• FDA posts a huge amount of information on fda.gov including a database of databases

• Sometimes this information is redacted to preserve confidentiality

• Examples:
  – Inspections Database
  – Searchable Warning Letters Database
  – Drugs@FDA
  – Inactive Ingredient Search for Approved Drug Products
  – Orange Book (Approved Drug Products with Therapeutic Equivalence)
  – Generally Recognized as Safe (GRAS) Substances Database
A Two-Way Street

• By looking at questions that arise repeatedly FDA can identify issues that need to be raised in general terms through guidances or outreach. Examples:
  – Stability Conditions
  – Naming conventions
  – Unidentified impurities

• By looking at the questions that they receive from FDA, industry can modify the contents of their applications
How have things changed over the years?

- Originally stability testing done at 25°C/60% RH, customary for the US.
- PEPFAR countries are mostly hot and humid so testing at 30°C/75% RH has been recommended.
- Storage statements such as “Store at room temperature below 30°C” are now common.
Other Changes

• A mechanism for post-Tentative Approval changes
• Extension of expiration based on the batches in the original application (which are not necessarily commercial scale)
• Stability data 6 months for 3 batches at submission
• Revised Guidance coming soon!
Competition is Good!

- More Tentatively Approved Applications
- More capacity
- More competition
- Lower prices (bottle of 30 generic Atripla tablets is $11.89)
- Cost per patient has declined from $1100 to $315 (less than half is the cost of drugs) (http://www.pepfar.gov/documents/organization/105842.pdf)
- 6.7 million people under treatment
Clinical Aspects

• In most PEPFAR countries treatment starts at CD4 < 350 (used to be 200).
• In the US treatment strongly recommended below 500 and many physicians treat immediately.
• Starting regimen usually one pill once a day such as Atripla.
• This applies both in US and in PEPFAR countries (Thanks to Dr. Jeff Murray, DAVP)
The Future?

- Revised guidance
- New combinations responding to clinical developments
- Manufacturing closer to the populations being treated
- Collaboration between FDA and local regulators
- FDA reaching out to manufacturers
- Pre-NDA interactions with FDA for PEPFAR applications
- Other diseases such as hepatitis
Questions? (newdrugCMC@fda.hhs.gov)

Approved and Tentatively Approved products:
http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm

PEPFAR Guidance:

SCMS website: http://scms.pfscm.org/scms
SCMS e-catalog: http://www.scms.pfscm.org/scms/ecatalog/arvs

PEPFAR information: www.pepfar.gov

Dissolution methods:
http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm

Database of databases:
http://www.fda.gov/forindustry/fdabasicsforindustry/ucm234631.htm

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Oh yeah…

• FDA is hiring: www.fda.gov/gdufahiring