Risk Management for ANDA Portfolio

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Outline

- What is at risk?
- What part of our portfolio does it effect?
- What specifically are the issues?
- What is mitigation plan?
- What are the overall issues?

What is the Risk?

- Products in our portfolio that are on the market and are under registration have elements of data that were fabricated to support business needs
  - Patient data in Bioequivalence studies
  - Stability data to support shelf life
  - Changes in formulation not intended for a specific country
- This issue is not just limited to ARV products, rather it is much more pervasive affecting more than 200 products in more than 40 countries
- We need to agree on a strategy to systematically address each issue and implement a risk mitigation plan as soon as possible

What is the Risk?

- This will have a significant impact on the revenues for the next two years
- We need to understand and address the legal liability for the company and the individuals in the company

Scope of the risk plan

- ARV product portfolio
  - For US (PEPFAR) & WHO
  - For ROW countries (Africas and Asia-Pac)
- Product portfolios (non-ARV products) for Middle East, Asia-Pac and the Rest of the World
- Certain products in our EU/CEE portfolio
- Brazil & Mexico portfolio

ARV Products

- Discrepancies in patient data in the BE studies that were submitted for registration (conducted at Vimta Laboratories)
- R&D batches were used for establishing stability of the product (no data was generated for batches taken at Dewas and/or other manufacturing locations)
- Registration package contained incorrect data on the size of the stability batches (e.g., 20K filed vs. 2K that was used to establish stability)
- Analytical data used to support registration is suspect (chromatograms do not exist)

ARV Products

- Significant deviations in the manufacturing process of approved products were not captured in production batch records
  - e.g., compacting, slugging, formulation changes etc.
- For some products, the production batches were transferred from Jejuri to Dewas, however, product stability study was not conducted at the new location. The product was subsequently filed from Dewas.
- Internal processes were not followed to ensure compliance with GLP, GMP and GCP

ARV Products

- For some products, the stability studies is contracted to an outside laboratory. The GLP/GMP compliance of this outside laboratory has been questioned by GQA
- API being used from Matrix labs Unit 1 will not pass a WHO inspection since it is not GMP compliant and processes and traceability of data and documents is questionable
- In ROW countries (e.g., Vietnam, Venezuela, Sri Lanka), stability data was made up since they require complete shelf life data as a part of registration dossier

ROW Portfolio

- Systematically, stability and BE studies were filed on formulations that was not intended for these markets since the data was not available
- Stability data filed with registration package does not exist for many products
- Patient data filed with registration package does not exist for many products
- BE studies were conducted on R&D lab batches

ROW Portfolio

- For some countries, the entire product portfolio is suspect with respect to the content of the data in the dossier
- We have also put our partners (Bayer & Merck in Mexico and in South Africa) at risk by using suspect data in our dossiers
- For many products, the manufacturing locations are Goa and Jejuri and loan license, which do not have processes that are consistent with Dewas and Paonta Sahib especially with respect to product stability monitoring

EU/CEE Portfolio

- In specific cases, stability data is suspect (chromatograms supporting shelf-life of the product were fabricated)
- In specific cases, API from a non-approved source was labeled as coming from an approved source and submitted for manufacturing
- In specific cases, manufacturing process was changed and the variation was not filed/documented
- For specific products, BE was conducted at Vimta Laboratories

Brazil & Mexico Portfolio

- Most of the bioequivalence studies for Brazil portfolio were done at Vimta Laboratories
  - Patient data filed with registration package does not exist in many cases
- Stability data filed with registration package does not exist in many cases
- BE Studies were performed on R&D laboratory batches as per acceptance from the country business head (this is not in line with local regulatory requirements)

Risk Factors

- WHO delisting of our ARV products is already spilling over to other areas
  - The Clinton Foundation's inspection of our manufacturing facility
  - Confidential information is being leaked which may lead to further audits and inspections
  - We can expect other countries to conduct their own independent, in-depth inspection of all our facilities
- Will have an impact on our Branded and NCE portfolio
  - Our ability to work with the US FDA, EMEA & MHRA
  - Our ability to attract partners and enter into alliances
- The impact on our reputation and goodwill can be significant

Risk Mitigation Strategy

Guiding Principles

- Patient Safety is our first responsibility
- Our products have to be proven safe and effective
- A short term loss of revenue is better than a long term losing proposition for the entire business
- Integrity of our business conduct in the interest of our long term growth
- Protect the company
  - Legal repercussions
  - Goodwill and reputation

ARV Products

- Repeat all BE studies at a reputed CRO/in-house
- Formalize changes in the manufacturing process to include all deviations. Transfer manufacturing location from Dewas to Paonta Sahib and execute the formalized process
- Repeat stability studies on properly executed exhibit batches
- Work with Matrix Labs to expedite the transfer of API manufacture to Unit 2 and institute processes to ensure GMP compliance at Unit 2
- Wait until stability data is available on properly executed exhibit batches to re-file with WHO and other agencies worldwide

ARV Products

- It is our regulatory obligation to inform other countries where we market ARVs about these issues
  - Withdraw any ARV product that is under registration
  - Withdraw any ARV product that has secured regulatory approval and is not launched yet
  - For those products already on the market, develop a strategy in agreement with regulatory agency that addresses our guiding principles and implement it immediately
- Proceed with regulatory filings only after all data is available for ROW countries from the proposed manufacturing location
  - In countries such as Vietnam, Venezuela and Sri Lanka, this would delay the launch by about 2 years

ROW Portfolio

- Withdraw any product in the list that is currently under registration
- Withdraw any product in the list that has secured regulatory approval and is not launched yet
- For those products already on the market, develop a strategy in agreement with regulatory agency that addresses our guiding principles and implement it immediately
- In cases we are marketing product that is different from that which was approved, we need to develop a strategy to tell the regulatory authorities as to how we intend to switch to the right product for that market

ROW Portfolio

- Repeat BE studies where data is suspect or were conducted with incorrect formulation
- Repeat stability studies on properly executed exhibit batches where data is suspect
- Strengthen the current stability monitoring program at Dewas, Mohali and Paonta Sahib
- Institute the right stability monitoring program for Jejuri and Goa and Loan License manufacturing locations

EU/CEE Portfolio

- Repeat any BE studies where patient data is suspect (all studies conducted at Vimta Labs) or were conducted with incorrect formulation
- Repeat all Stability studies where chromatograms were made up
- Develop a strategy to file a variation with the health authorities where API was from a different source than what was submitted

Brazil & Mexico Portfolio

- Repeat all BE studies conducted at Vimta Labs with a reputed CRO
- Conduct a QA audit on BE study reports conducted at any CRO
- Repeat all BE studies that were conducted with incorrect formulation
- Conduct Zone IV and Zone II stability studies for all products filed since 2001 with properly executed exhibit batches

Brazil & Mexico Portfolio

- Do not offer any dossier to any partner until we have all studies completed in a regulatory compliant manner
- Withdraw all products currently under registration with suspect BE, Stability or Manufacturing data
- Develop a strategy to address dossiers shared with partners containing suspect data consistent with our guiding principles

Overall Issues

- We need a SWOT team to develop & implement strategies for the various markets/portfolios based upon the recommendations made. This must be completed in the next 60 days
- Appropriate direct cost and FTEs should be allocated as a priority to address this effort and the subsequent implementation of the strategy
- Timelines for re-filing of withdrawn products under registration or products already on the market should be made consistent with the guiding principles

Overall Issues

- This will have a short-term negative impact on revenues for 2005 and 2006
- Institute processes for checks and balances so that we adhere to the regulatory guidelines and conform to ICH
- Undertake a legal evaluation and understanding of the impact of these findings