

# INTRODUCTION

- There is continuing interest in the **development, U.S. FDA approval** and **importation** of foreign drugs into the U.S. market.
- The existing FDA regulations continue to place significant challenges on both foreign and U.S. manufacturers.
- Foreign companies are subjected to the **same FDA scrutiny** as the U.S. companies.

- The importation of foreign drugs needs to comply with regulations because FDA has become more **enforcement-minded but with a twist.**
- Although the drug development process may be similar in different regions, **differences** due to culture, medical practice, demographics and other factors can impact how and how rapidly new drugs gain access to different markets.
- The agency is increasingly concerned about the **GMP compliance** in the manufacturing of APIs used in the U.S.

# REGULATORY FRAMEWORK

Two regulatory entities

- **The U.S. Food and Drug Administration (FDA) :**  
it sets the criteria for acceptance.
  
- **The International Conference on Harmonization (ICH) :**  
it addresses the issue with specific guidelines and CTD.

## U.S. Food and Drug Administration

- FDA regulations governing the approval of a new drug to market are covered in the Code of Federal Regulations ([CFR](#)), [Title 21, Part 314](#).
- If the agency feels that the criteria listed have been met it may approve the product based on foreign studies.
- The FDA has approved approximately [80 drugs](#) based solely on clinical data generated outside the United States.

## International Conference on Harmonization

- ICH has examined ways to help make clinical data collected in one region acceptable to the regulatory authority of another region.
- An outcome of this ongoing effort is the ICH guideline **E5, "Ethnic Factors in the Acceptability of Foreign Clinical Data."**
- For sponsors of foreign drugs, ICH guidelines E5 complements the FDA regulations.
- It notes that all data in the clinical section should meet the standards for study design and conduct and should satisfy the regulatory requirements of the region.

- Once that has been accomplished, the sponsor must be able to **extrapolate the study data** to the population of the new region, in this case, the United States.
- If the sponsor or the regulatory agency is concerned that ethnic differences could have a significant impact on the safety or efficacy of the drug in the new population, additional data may be necessary.
- The core concept of ICH guideline E5 is the “[bridging study](#).”

## POTENTIAL OBSTACLES

The issues that sponsors of foreign drugs must address fall into three broad categories

- **CMC** (Chemistry, Manufacturing, and Control) **Issues**
- **Nonclinical Issues**
- **Clinical Issues**

## 1. Chemistry, Manufacturing and Control Issues

- ✓ The FDA requires the same CMC information for foreign drugs as it does for unapproved new domestic drugs.
- ✓ All drug manufacturers must comply with cGMPs for finished pharmaceuticals as specified in 21 CFR 211.
- ✓ Manufacturers must meet USP standards for the drug substance, its excipient or the drug product, if available.
- ✓ Sponsors of foreign drugs should follow ICH quality guidelines regarding stability, validation of analytical procedures, acceptable levels of impurities, residual solvents, etc



- ✓ Sponsors may submit information regarding the chemistry and manufacturing of drug substances, products, excipients or packaging in a [Drug Master File \(DMF\)](#).

## *Importation procedures and related issues*

- Foreign manufacturers must register with the FDA's **Drug Listing Branch** and have a drug establishment number assigned to them.
- In order to import a foreign drug product through U.S. customs, the importer should provide **relevant documentation**.
- Foreign manufacturers must also have a **U.S. agent** who resides in or maintains a physical place of business in the United States.

## *FDA inspections of foreign manufacturers*

- The FDA may **inspect** a foreign manufacturing site.
- If the FDA conducts an inspection and finds problems, the inspector will report his or her observations of the conditions and practices observed at the site on **FDA Form 483**.

## 2. Nonclinical Issues

- ✓ The data must demonstrate **safety** for human subjects during clinical trials and for patients when the drug is marketed.
- ✓ The ICH guideline **M3, “Timing of Pre-clinical Studies in Relation to Clinical Trials,”** addresses general considerations in regard to when nonclinical studies are conducted in a drug development programme.
- ✓ In order for the foreign nonclinical data to be acceptable to the FDA, the testing must be conducted according to Good Laboratory Practices (GLPs, found in 21 CFR 58).

- ✓ The drug substance and drug product, or formulation, tested in the nonclinical studies should be relevant to the product that the sponsor intends to market in the United States.
- ✓ The final safety database should reflect **known safety concerns** that have been observed in either animals or humans throughout drug development.
- ✓ It is important that the sponsor conduct the nonclinical testing in species whose **ADME** are **relevant to humans**.

### 3. Clinical Issues

By planning to address intrinsic and extrinsic ethnic differences throughout the drug development process, the sponsor of a foreign drug may

- ✓ **save time**

- ✓ **reduce the need to replicate studies**

and build a stronger case for FDA acceptance.

## *Investigator/site selection*

- **Selected investigators** must be familiar with conducting controlled clinical trials according to Good Clinical Practice (GCP) guidelines.
- **Selected sites** should have sufficient research training and experience in conducting trials that may eventually be audited by the FDA.
- **Control** of investigational drug product and control over the conduct of the investigation are essential for U.S. registration.

## *Drug–drug interactions*

- Drug–drug interaction data from foreign studies may have limited utility in the United States.
- A wide range of factors may complicate the extrapolation of foreign data to support labeling for the U.S. population.
- The sponsor and ultimately the FDA may determine that **additional drug–drug interaction trials** may be necessary to support U.S. labeling.

## *Patient issues*

- Study treatment compliance or lack can also be a barrier to acceptance of foreign data.
- In populations with low levels of education it can be difficult to assure patient compliance.



## *Choice of comparator and dose*

- The relevance of foreign clinical data may also be judged by the choice of comparator as well as relevant dose or dose range for both test and comparator drugs.
- The choice of dose and dosage of a drug in a pivotal trial that is used to support a U.S. application should also be carefully considered.

# DATA SUBMISSION

- A description of the investigator's qualifications
- A description of the research facilities
- A detailed summary of the protocol and results of the study and case records maintained by the investigator
- A description of the drug substance and drug product used in the clinical study

## CONCLUSION

- ✓ Development of a foreign drug for approval in the U.S. market is similar to the development of U.S. drugs.
- ✓ Regardless of where the drug originates or where data were collected, sponsors must meet the **same requirements**.
- ✓ Companies that develop foreign drugs must **plan carefully** and **communicate** with FDA **“early and often”**.
- ✓ Drug development is challenging for pharmaceutical companies everywhere. The **“foreign”** element may complicate the process somewhat but it is not an insurmountable obstacle.

**FDA**  
**APPROVED**