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## Expediting Drug Development in the US

- **Session Objectives**
  - We will discuss the following topics and ways to expedite drug development
    - General Considerations
    - Role of the Package Insert in Drug Development
    - Chemistry/Manufacturing/Control Issues
      - Packaging
      - Marketing
    - Toxicology Issues
    - Clinical Issues



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## *Expediting Drug Development in the US*

### ☐ General Considerations

- Know the needs of your customer – The regulatory authorities
- Do not guess – Base decisions on facts/data
- Establish an experienced project team – It is important that they not only know their own job functions well but the interplay between departments
- Development plans need to be dynamic
  - Successful and timely drug development is the ability to quickly solve one problem after another



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## *Expediting Drug Development in the US*

### ☐ General Considerations

- Project Management versus Project Tracking
  - Know the difference (in drug development, lost time is never found)
- Realistic Timelines
  - Make the timeline challenging but realistic
  - Allow/recognize that problems will occur
- Submission Date
  - Better to project than to fix the date
- The goal is approval....not submission



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## ***Expediting Drug Development in the US***

### **❑The Project Team (deliverables)**

- **Marketing (promotional material)**
- **Pharmacology (general/safety pharmacology)**
- **Toxicology (preclinical safety studies)**
- **Pharmacokinetics (preclinical, clinical)**
- **Production (drug substance)**
- **Pharmaceutics (dosage form development)**



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## ***Expediting Drug Development in the US***

### **❑The Project Team (disciplines)**

- **Manufacturing (drug product)**
- **Analytical Chemistry (test methods, stability)**
- **Clinical Research (data management, biostatistics, programming)**
- **Legal (patent issues)**
- **Regulatory Affairs (regulatory interactions, electronic submissions)**



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## ***Expediting Drug Development in the US***

### **❑ Fast Track – What it is**

- **A series of programs for expediting drug development and application review**
  - **Meetings**
  - **Written Correspondence**
  - **Review Programs (e.g., rolling review)**
  - **Dispute Resolutions**
- **For serious conditions and have the potential to address an unmet medical need, so the majority of drugs being developed to not comply**



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## ***Expediting Drug Development in the US***

### **❑ Fast Track – What it is not**

- **A shortcut**
- **Fast Track does not eliminate the need for**
  - **Pharmacology**
  - **Toxicology**
  - **Chemistry/Manufacturing/Controls**
  - **Clinical Research**
- **All of the disciplines required to write a Package Insert are still required**



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## ***Expediting Drug Development in the US***

### **❑ The Package Insert as a Drug Development Tool**

- **Drafting the Package Insert (or Target Product Profile) early on**
  - **Prompts consideration of all facets of drug development**
  - **Is key to efficient drug development**
  - **Should be written first (rarely done)**
  - **Resist “To be determined”**
  - **Can assist with generating timelines and costs**
  - **Remember, it is a dynamic document**
  - **An annotated Package Insert, with supporting study protocols appended, can serve as the development program**



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## ***Expediting Drug Development in the US***

### **❑ The Package Insert as a Drug Development Tool**

- **Annotated Package Insert**
  - **Required at NDA time**
  - **Annotations are used to identify studies that support claims/statements in the Package Insert**
  - **For example: “Wonder Drug is indicated for the treatment of hypertension<sup>1,2</sup>”**
    - **1: Study Report 123 entitled “A 12 week study of Wonder Drug for the treatment of mild to moderate hypertension”**
    - **2: Study Report 456 entitled: “A 52 week study of Wonder Drug for the treatment of mild to moderate hypertension”**



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## » Expediting Drug Development in the US

### ❑ The Package Insert as a Drug Development Tool

#### ➤ INDICATIONS AND USAGE

- Probably the most important aspect of Package Insert as it relates to the development program
- The indication
  - Is necessary for the design of the clinical program
    - Palliation vs treatment vs prevention
    - Establishes inclusion/exclusion criteria
    - Severity of disease
    - Comparative claims
  - Determines the toxicology needs of the program
- Usage
  - Impacts dosage form (oral vs IV)
  - Intravenous formulation (compatibility of infusion sets, stability with infusion sets, ancillary devices, etc.)



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## » Expediting Drug Development in the US

### ❑ The Package Insert as a Drug Development Tool

#### ➤ DOSAGE AND ADMINISTRATION

- Based on results of Phase 1, 2 and 3 studies
- Ensure that clinical studies are designed to provide adequate instructions for use
  - Food effects
  - Dosing interval (for example, b.i.d, t.i.d)
  - Minimally effective dose
  - Drug interactions

#### ➤ DOSAGE FORMS AND STRENGTHS

- Tablet versus capsule
  - Ensure Phase 3 trials use the to-be-marketed formulation
- What is the desired dosing interval
  - May impact design (slow release) or strength of dosage form
- Convenience to patient



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## » Expediting Drug Development in the US

- ☐ The Package Insert as a Drug Development Tool
- ☐ CONTRAINDICATIONS
  - ☐ Based on pharmacological class
  - ☐ Consider
    - ☐ Potential hypersensitivity
    - ☐ Age
    - ☐ Gender
    - ☐ Allergies
    - ☐ Concomitant medications
      - ☐ Drug-drug interaction studies (very important)
- ☐ WARNINGS AND PRECAUTIONS
  - ☐ Information to patients (driving a car, concomitant medications)
  - ☐ Necessary laboratory tests before/during use
  - ☐ Toxicology findings (carcinogenicity, pregnancy, lactating women)
  - ☐ Hepatically/renally impaired patients
  - ☐ Geriatric use (dose reduction?)



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## » Expediting Drug Development in the US

- ☐ The Package Insert as a Drug Development Tool
  - ADVERSE REACTIONS
    - Identify potential AEs based on toxicology studies
      - Incorporate into clinical protocols
      - Any special laboratory tests or monitoring required
      - Generally based on Phase 3 study results
  - DRUG INTERACTIONS
    - Have possible drug-drug interactions been studied
      - Preclinical/clinical *in vivo* and *in vitro* studies
      - Concomitant medications generally evaluated in Phase 3 studies
  - USE IN SPECIFIC POPULATIONS
    - Pregnancy (toxicology studies)
    - Lactation (toxicology studies)
    - Pediatric Use (pediatric plan)
    - Geriatric Use (renal function)



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## ***Expediting Drug Development in the US***

### **❑ The Package Insert as a Drug Development Tool**

#### **➤ OVERDOSAGE**

- Is it likely due to pharmacological class?
- Potential for abuse
- Steps to take/remedies

#### **➤ DESCRIPTION**

- Proprietary/generic names (apply early)
- Qualitative description of ingredients (are excipients GRAS?)
- Pharmacological/therapeutic class
- Chemical name/structural formula



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## ***Expediting Drug Development in the US***

**Break.....**



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## » Expediting Drug Development in the US

### ❑ The Package Insert as a Drug Development Tool

#### ➤ CLINICAL PHARMACOLOGY

- Mechanism of action
  - Based on pharmacology and clinical pharmacology studies
- Pharmacodynamics
  - Include necessary endpoints in clinical studies
- Pharmacokinetics
  - Based on Phase 1, 2, and 3 clinical studies
    - MTD (not just for oncology studies)
    - Rate and extent of absorption
    - Duration of action/dosing interval
    - Concentration-effect (for both efficacy and safety)
    - Half-life
    - Distribution
    - Metabolism/metabolites
    - Passage through blood brain barrier
    - Food effects



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## » Expediting Drug Development in the US

### ❑ The Package Insert as a Drug Development Tool

#### ➤ NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility
- Indication will determine the need for toxicology studies
  - Will long term (9 month dog/12 month rodent) toxicology studies be required
  - Long term use requires carcinogenicity and mutagenicity studies
    - Consider Special Protocol Assessment for carcinogenicity studies
  - Are woman of child-bearing potential likely to use the drug?
  - FDA also concerned about drug effect on male fertility
- Identifying the toxicology needs early on will allow for appropriate timing of studies relative to the ongoing clinical program



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## **>> Expediting Drug Development in the US**

### **❑ The Package Insert as a Drug Development Tool**

#### **> CLINICAL STUDIES**

- > FDA generally requires two or more adequate and well-controlled trials**
- > Outline the AWC trials (generally Phase 3 studies) that support the indication**
- > Outline pediatric studies in the pediatric study plan**
- > Outline the dose-ranging studies (generally Phase 2) that will support the Phase 3 studies and the doses to be used**
- > Outline the Phase 1 studies that will support the Phase 2 studies (drug interactions, food effects)**
- > Include the need for overall exposure (number of patients) in development program (ICH guidelines)**
  - > Usually “easier” (fewer subjects) to demonstrate efficacy**
- > The above outline of studies will allow for planning (timing, cost, etc.) of clinical program**



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## **>> Expediting Drug Development in the US**

### **❑ The Package Insert as a Drug Development Tool**

#### **> HOW SUPPLIED/STORAGE AND HANDLING**

- > Strength of dosage form**
- > Units (tablets/bottle)**
  - > Impacts stability program**
- > Shape, color, coating, NDC#**
- > Handling/storage conditions**
  - > Room temperature or refrigerated**
  - > Impacts stability program**



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## ***Expediting Drug Development in the US***

### **❑ The Package Insert as a Drug Development Tool**

#### **➤ PATIENT COUNSELING INFORMATION**

- Precautions should a particular adverse event occur
- Instructions on proper use (driving, use of heavy machinery)
- Overdose
- Storage



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## ***Expediting Drug Development in the US***

### **❑ The Package Insert as a Drug Development Tool**

#### **➤ Animal pharmacology/toxicology**

- Although not required, include in draft Package Insert to highlight needs of pharmacology to support scientific rationale of the development program and the toxicology program to support the claim
- Duration of the toxicology studies
- FDA has adopted ICH pharmacology/toxicology guidelines required for drug development



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## ***Expediting Drug Development in the US***

- ❑ **Considerations for expedited drug development**
  - ❑ **Chemistry/Manufacturing/Controls (Quality)**
    - **Ideally, FIX the following as soon as possible:**
      - **Starting material, method of manufacture**
      - **In-process controls**
      - **Analytical methods/laboratory**
      - **Container/closure system**
      - **Suppliers**
      - **Contractors**
    - **Above should be discussed at End-of-Phase 2 Meeting**
    - **Will allow for real-time stability data to be generated during Phase 3**



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## ***Expediting Drug Development in the US***

- ❑ **Considerations for expedited drug development**
  - **Chemistry/Manufacturing/Controls (Quality)**
    - **Process transfer and scale-up issues are extremely rate limiting**
    - **Early production experience may lead to batches that do not qualify**
    - **If using an outside vendor, have third party examine DMF – Remember one loses control if DMF is involved**



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## ***Expediting Drug Development in the US***

- ❑ **Considerations for expedited drug development**
  - **Chemistry/Manufacturing/Controls (Quality)**
    - **Production Issues**
      - **Changes in process can result in change in impurity/residual solvent profiles which can impact**
        - **New degradants?**
        - **Need for new methods?**
        - **Stability of drug substance/drug product?**
        - **Changes in finalizing drug substance will delay drug product manufacturing process validation**
        - **Additional preclinical/toxicology trials?**
        - **Safety in clinical trials?**
        - **Additional bioequivalence/bioavailability studies?**



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## ***Expediting Drug Development in the US***

- ❑ **Considerations for expedited drug development**
  - **Analytical Laboratories**
    - **Until drug substance and drug product processes are fixed, one can not**
    - **Finalize analytical methods**
    - **Validate the methods**
    - **Finalize methods transfer (if necessary)**
    - **Changing methods negatively impact stability program**



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## ***Expediting Drug Development in the US***

### **❑ Considerations for expedited drug development**

#### **➤ Package Design**

- **Conduct photosensitivity studies early on. Even if drug substance is insensitive to light, drug product might be sensitive**
- **Changes in suppliers of primary packaging, especially for parenteral products, can be very rate-limiting (appearance of leachables)**
- **Do not overlook secondary/tertiary packaging. If these components bear graphics or printed material, they are considered part of labeling.**



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## ***Expediting Drug Development in the US***

### **❑ Considerations for expedited drug development**

#### **➤ Toxicology**

- **Toxicology studies conducted with early batches (small) may not suffice**
  - **As you scale up drug substance production for clinical trials, the process may change, impurity profile may change, degradation products may change requiring additional toxicology studies**
- **Chronic toxicology/carcinogenicity studies can not be hurried**
- **Reproductive toxicology studies could limit enrollment of WCBP**
- **Getting toxicology studies off the critical path is business risk**



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## ***Expediting Drug Development in the US***

- ❑ **Considerations for expedited drug development**
  - **Clinical Research**
    - **Phase 1**
      - If possible, use expected patient population
        - Use “older” subjects if product is for the geriatric population or “younger” subjects for pediatric products
    - Main goal of Phase 1 studies is to identify both safe and unsafe doses
    - Define the maximally tolerated dose
    - FDA favors logarithmic dosing (1, 10, 100)
    - FDA regulations and guidelines are written to afford flexibility in the design and conduct of Phase 1 studies to minimize the need for protocol amendments (and IRB/EC approval)



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## ***Expediting Drug Development in the US***

- ❑ **Considerations for expedited drug development**
  - **Clinical Research**
    - **Phase 2**
      - Design studies for success
        - Use inclusion/exclusion criteria to identify subjects that are most likely to demonstrate effectiveness
      - Include adequate dose-ranging
        - Want to make sure your Phase 3 trials include minimally effective dose
    - Should be hypothesis-generating



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## ***Expediting Drug Development in the US***

- ❑ **Considerations for expedited drug development**
  - **Clinical Research**
    - **Phase 3**
      - **Hypothesis-confirming**
      - **Should not fail because of efficacy**
        - **Except for durability of response**
      - **Designed to allow for potential drug interactions to be studied**
      - **Critical for the writing of the CLINICAL STUDIES section of the Package Insert**



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## ***Expediting Drug Development in the US***

- ❑ **Considerations for expedited drug development**
  - **Marketing**
    - **Fix product's market image**
    - **Changes in color, inks, shape, engraving, size, and/or scoring can lead to delays and the need for bioequivalence studies**
    - **Fix packaging presentations. Include physician samples and promotional drug product materials in stability program**
    - **Changes in fill size or pill count will impact stability program**



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## *Expediting Drug Development in the US*

### ❑ Considerations for expedited drug development

#### ➤ Summary

- Establish an experienced team
- Do not guess
- Consider allowing the Package Insert to drive the process
- Realize that problems will occur
- Set challenging but realistic timelines
- The goal is approval - not submission
- Surest way to expedite drug development is good science



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