FDA REVIEW PRINCIPLES

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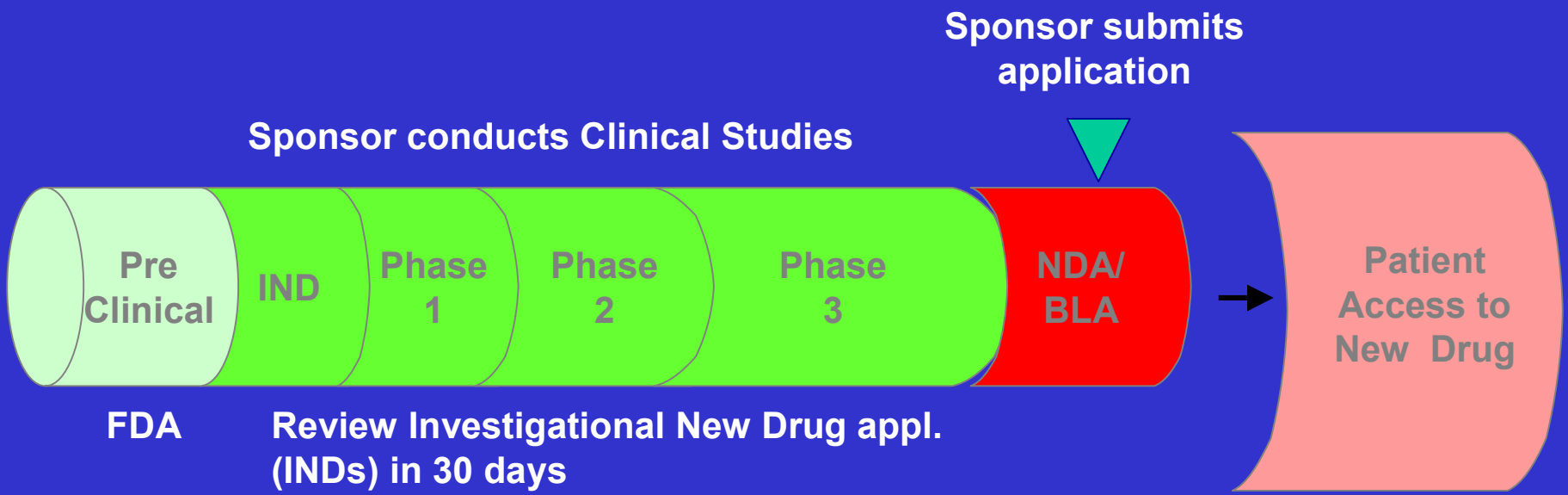
AFSSAPS

FDA REVIEW PRINCIPLES

- « A well-managed review process for an NDA or BLA begins with interactions between the applicant and the Agency's therapeutic division having primary responsibility for regulatory actions on the product (review division) during the **drug development (IND) phase and continues through the final action on the marketing application** «

  - **FDA Guidance for Review Staff: Good Review Management Principles for PDUFA Products, July 2003, Procedural**

NDA/BLA Review Time/ PDUFA III Goals: Shorten Clinical Development



FDA

Review Investigational New Drug appl. (INDs) in 30 days

Hold meetings with sponsors within 30/60/75 days of request

Respond to clinical holds within 30 days

Evaluate special protocol designs, at request of sponsor, within 45 days

FDA review

Priority applications in 6 months

Standard applications in 10 months

Modified from J. Jenkins MD

FDA REVIEW TEAM

- **Regulatory Project Manager (RPM)**
  - Medical/clinical
  - Pharmacology/toxicology
  - CMC
  - Biometrics/statistical
  - Clinical pharmacology and biopharmaceutics
  - Clinical microbiology
  - Consultants

PROCESS PRINCIPLES

- **Milestone Meetings**
  - **End of phase II**
  - **Pre-NDA/BLA submission:**
    - **6 to 12 months prior to submission**
    - **Comprehensive summary of relevant data generated during development**
    - **Discuss all critical issues(that may affect ability to review/approve the application)**
  - **Special Protocol Assessment**

PROCESS PRINCIPLES

- **Communication between FDA and Applicant during review**
  - **The RPM is the FDA point of contact**
  - **FDA will convey readily correctable issues as they are identify which should be addressed quickly**
  - **Filing review issues are conveyed to applicant**
  - **Communication through secure e-mail is encouragedI**
  - **Information Request(IR) Letters identify the need for additional data or request clarification to facilitate the review**
  - **The decision to present to an Advisory Committee (AC)is made by the review division. The AC becomes an integral part of the review process**

PDUFA PERFORMANCE GOALS

- **PDUFA**(Prescription Drug User Fee Act)**authorizes FDA to collect fees from the pharmaceutical industry to augment financial resources spent on drug review**
- **PDUFA regulates FDA procedural and processing goals :**
  - **Submissions and resubmissions review**
  - **Meeting management**
  - **Clinical holds**
  - **Major dispute resolution**
  - **Special protocol assessment**
  - **Continous marketing application**

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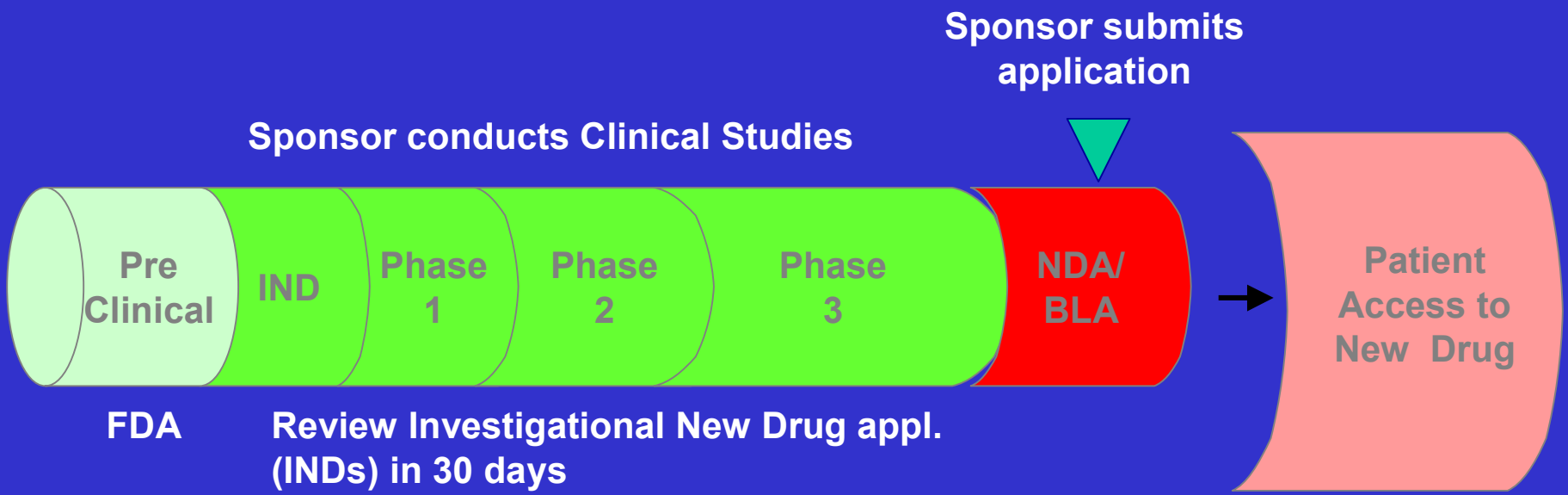

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PROCESS PRINCIPLES

- **Priority Review Policy :**
  - **Definition: product that would be a significant improvement compared to marketed products or existing therapies**
  - **Improvements are :**
    - **Increased effectiveness in treatment, prevention or diagnosis**
    - **Substantial reduction of a treatment-limiting drug reaction**
    - **Enhancement of patient compliance**
    - **Safety and effectiveness in a new subpopulation**
  - **Decision is made for every application submitted, regardless of applicant request**
  - **Designation after application receipt and no later than 60 days**

PROCESS PRINCIPLES

- **Level of review**
  - **Classic « bottom up » approach**
  - **Standard submission includes :**
    - **Raw statistical data eg SAS data set**
    - **Key parameters of pk/pd modelling**
    - **Copies of individual CRFs of deaths, discontinuations and serious AEs**
  - **Generally main results are reanalysed with re-computation of raw data**
  - **Often during review more detailed information is requested although the content of the submission is agreed at the pre-NDA meeting**

ADVISORY COMMITTEE

- **Advisory committees(AC) provide independent advice and recommendations**
- **Reviewing division decision for :**
  - **New class of drugs**
  - **Novel or surrogate clinical end-points**
  - **Critical issues in drug safety/effectiveness**
  - **Public health questions on the role of drug in the disease treatment**
- **Complex and time sensitive logistics**
- **Briefing package(FDA and sponsor) for the AC members is available for the public**

PROCESS PRINCIPLES

- **End of the first-cycle review :**
  - **Within the PDUFA review goal timeline**
  - **FDA provides action letters : product approved or complete response letters(approvable/nonapprovable) with list of deficiencies**
  - **Approvable application: deficiencies range from labeling comments to completion of additional clinical trials**
  - **Non-approvable application more serious deficiencies with need of significant additional work**
  - **Review of NDA/BLA resubmissions (Class 1 or 2) within 2 to 6 months**

PROCESS PRINCIPLES

- **Fast Track Drug Development: two regulations**
  - **Accelerated Approval, CFR 314.500 Subpart H :**
    - Approval on surrogate end-points
    - Expedite review process
    - Restrictions to assure safe use
  - **Fast Track, FDAMA section 112:**
    - Early consultations during drug development
    - Fast track procedure for whole development process
    - Rolling submissions
    - Surrogate or final end-points

Pilot Programs for Continous Marketing Application

- **Pilot 1 - Expansion of rolling NDA reviews**
  - **Limited to Fast Track drugs and biologics**
  - **FDA/sponsor agreement to pre-submission of "reviewable units" of NDA/BLA**
  - **6-month review clock for each RU with phased-in performance goals**
  - **FDA feedback to sponsor in the form of a discipline review letter**
  - **Guidance in development; target program start date of October 1, 2003**

Pilot Programs for Continous Marketing Application

- **Pilot 2 - Expansion of interactions during drug development (IND phase)**
  - **Limited to Fast Track drugs and biologics**
  - **Starts as early as end-of-phase 1 meeting**
  - **Only one product per "review division"**
  - **Agreement between FDA and sponsor on types of interactions**
  - **Guidance under development, target start date of October 1, 2003**