CDER Forum for International Drug Regulatory Authorities
Good Review Practices (GRPs) in the United States

FDA-CDER
Office of New Drugs-Immediate Office
Guidance and Policy Team
Howard D. Chazin, M.D., M.B.A.

Why Good *Review* Practices?

Other regulations that help FDA do its job…

- **Current Good Manufacturing Practices (cGMP)**
- **Good Clinical Practice (GCP)/ICH E6**
- **Good Guidance Practices (GGP)**
- **Good Review Management Principles and Practices (GRMP)**

CDERs GRPs

- **A *documented best practice* within CDER that discusses any aspect related to the process, format, content, and/or management of a product review.**
- **GRPs are developed over time as superior practices based on CDER's collective experience to provide consistency to the overall review process of new products.**

Fundamental Values

- **GRPs all share several fundamental values.**
  - **Quality**
  - **Efficiency**
  - **Clarity**
  - **Transparency**
  - **Consistency**

CDER Forum for International Drug Regulatory Authorities

Quality

- **Consistent implementation of GRPs by review staff will enhance the quality of reviews, the review process, and the resultant regulatory action.**

Efficiency

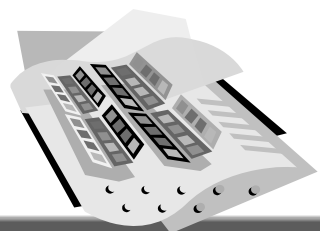
- **GRPs will improve the efficiency of the review process through standardization.**

Clarity

- **GRPs support clarity throughout the review process, including critical review and decision activities that must be completed before a regulatory decision is made.**

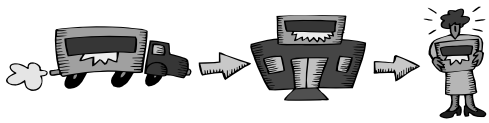
Transparency

- **Developing and documenting GRPs ensures that our review processes are readily available in one location via the Internet (through CDER's Web site) to sponsors and the public.**



Consistency

- **By offering a consistent approach and only deviating from it when appropriate (after supervisory concurrence), GRPs help reviewers achieve consistency with their reviews and provide standard review processes across divisions and offices.**



Why are GRPs developed?

To identify, collect, enhance, implement, and adopt many best practices as documented and standardized practices that can be shared among all review divisions.

- **Based on experiences within individual review divisions.**
- **As a response to changing regulatory environments (e.g., the Prescription Drug User Fee Act)**
- **To formulate an overall quality systems approach to product review**

GRP vs Guidance vs MAPP

- **GRPs educate review staff and industry and have been released in many forms:**
  - ***Guidance for Industry and Reviewer Staff***
  - ***Reviewer Guidance***
  - ***Manual of Policies and Procedures (MAPPs)***

Future GRPs will be MAPPs or Guidance for Industry and Review Staff (hybrid Guidance/MAPP)

MAPP or Hybrid Guidance/MAPP

- **Not all MAPPs are GRPs. Only the best practices become GRPs.**
  - **Most GRPs, however, are MAPPs- they inform review staff how to better perform their jobs.**

Hybrid Guidance/MAPP GRP

- Some GRPs also instruct sponsors and are part guidance and part MAPP (Hybrid Guidance/MAPP). These are treated like guidances from the sponsor perspective and contain nonbinding recommendations.
- From the review staff perspective, the hybrid Guidance/MAPP is considered a MAPP and is to be followed by review staff unless they receive supervisory instruction to do otherwise.

GRP documents are important!

- Sponsors should become familiar with CDER's GRP documents to better understand CDER's internal processes and the expectations of our review staff.

GRPs in Summary…

- **Provide a more consistent approach to the review and approval of new products**
- **Specify our process, format and content of a review**
- **Help standardize reviews and review management**
- **Help us train staff and inform industry of our internal review best practices**

Existing GRP examples

- *Reviewer Guidance-Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review*
- *MAPP 6010.3 Clinical Review Template*
- *Guidance for Reviewers Pharmacology/Toxicology Review Format*
- *MAPP 4000.4 Clinical Pharmacology and Biopharmaceutics Review Template*
- *Guidance for Review Staff and Industry Good Review Management Principles and Practices for PDUFA Products*

Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review

- **Issued February 2005**
- **Collaborative effort across CDER: Office of New Drugs, Office of Drug Safety, Office of Medical Policy.**

Purpose of the NDA Clinical Safety Review GRP

- **Assist reviewers conducting the clinical NDA/BLA safety review**
- **Describe Good Review Practices (GRP) for a premarketing safety review**
- **Provide Standardization and Consistency of format and content**
- **Ensure critical presentations and analyses of safety data are not omitted**

Content of the NDA Clinical Safety Review GRP

- **Advice on how to conduct and organize the safety review section of the NDA/BLA review**
- **Annotated Outline of the safety component of the clinical review of an NDA/BLA**

Content of the NDA Clinical Safety Review GRP
Four Principal Tasks

1. **Identify serious AEs that could:**
   - **Prevent use altogether**
   - **Limit use**
   - **Require special risk management efforts**
2. **Estimate frequency of common AEs**
3. **Evaluate adequacy of the data and the analyses (e.g., was exposure at relevant doses adequate?)**
4. **Identify unresolved safety concerns that need further attention (either pre-approval, or during post-marketing)**

Organization of the NDA Clinical Safety Review GRP

Four Sections

- **Review of the safety data (how did the applicant assess safety, and what were the findings?)**
- **Adequacy of the applicant's safety evaluation**

7.1
Methods and Findings

7.2
Adequacy of Patient Exposure and Safety Assessment

Organization of the NDA Clinical Safety Review GRP

7.3
Summary of Selected Adverse Reactions, Important Limitations of Data And Conclusions

- **Summary and Conclusions**

7.4
General Methodology

- **Review Methods**

Section 7.1 Methods and Findings

- Discusses the relevant data sources
- Evaluates safety assessments that were conducted
- Summarizes and considers major safety findings
- Utilizes a systematic approach to the review

Section 7.1 Methods and Findings

7.1.1 Deaths
7.1.2 SAEs
7.1.3 Adverse dropouts, other significant AEs
7.1.4 Other Search Strategies
7.1.5 Common AEs
7.1.6 Less Common AEs
7.1.7 Laboratory Findings
7.1.8 Vital Signs
7.1.9 ECGs
7.1.10 Immunogenicity
7.1.11 Human Carcinogenicity
7.1.12 Special Safety Studies
7.1.13 Withdrawal / Abuse
7.1.14 Repro / Pregnancy
7.1.15 Effect on Growth
7.1.16 Overdose
7.1.17 Postmarketing Experience

Section 7.2 Adequacy of Patient Exposure and Safety Assessments

- **Was patient exposure adequate? (e.g., overall numbers, duration, dose levels, in specific subgroups)**
- **Quality and Completeness of the safety evaluation (animal tests, in vitro tests, long-term safety testing, specific assessments)**
- **Are additional safety testing needed, either pre-approval or post-marketing?**

Section 7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Data Sources (populations exposed, extent of exposure)
7.2.2 Description of 2^{o} Data Sources
7.2.3 Adequacy of Overall Clinical Experience
7.2.4 Adequacy of animal/in vitro testing
7.2.5 Adequacy of Routine Clinical Testing
7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup
7.2.7 Recommendations for Further Study

Section 7.3 Summary of Selected AEs, Important Limitations of Data, and Conclusions

- Brief summary of the critical findings of the safety review
- Contains AEs that the review considers important and drug-related
- Summary of important limitations of the safety database
- Safety conclusions

Section 7.4 General Methodology

- Describes analytical methods used in the safety review
- General discussion of methodological issues not discussed elsewhere
  - 7.4.1 Pooling Data Across Studies
  - 7.4.2 Exploration for Predictive Factors
  - 7.4.3 Causality Determination

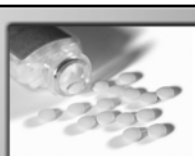
CDER Forum for International Drug Regulatory Authorities

Summary of the NDA Clinical Safety Review GRP

- Final guidance on how to conduct a clinical NDA/BLA safety review
- Provides standardization and consistency of format and content of the safety review
- Ensure critical presentations and analyses of safety data are not omitted
- Harmonized with the Clinical Review Template described in a companion MAPP/GRP document.

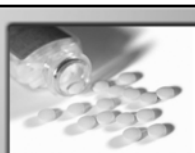
GRPs- constantly updated

- GRPs are expected to be updated quickly and frequently to reflect the ever changing regulatory and scientific environments.
- Advances in information technology (e.g., the Internet and FDA Web pages) over the past decade offer excellent mechanisms for documenting and implementing GRP policies.



Acknowledgements

- John Jenkins, M.D. – Director, Office of New Drugs
- Robert Temple, M.D. – Director, Office of Medical Policy
- Armando Oliva, M.D. – Associate Director for Policy, Office of New Drugs
- Judy Racoosin, M.D. – Safety Team Leader, Division of Neurology Drug Products



Contact Info

Howard Chazin, M.D., M.B.A.

FDA-CDER

Office of New Drugs

Guidance and Policy Team

(301) 796-1053

howard.chazin@fda.hhs.gov

CDER Forum for International Drug Regulatory Authorities