

FDA'S DRAFT GUIDANCE ON MULTIPLE ENDPOINTS IN CLINICAL TRIALS: OVERVIEW, RECEPTION AND NEXT STEPS

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Disclaimer

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Outline

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- Overview of FDA's draft Guidance on Multiple Endpoints in Clinical Trials
- Summary of major public comments received
- Discussion of questions raised and outstanding issues toward finalization of the Guidance

FDA approval standards

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- Drugs and biologics need to be “safe and effective” to be approved
 - ▣ Biologics also need to be “safe, pure and potent”
- “Substantial evidence” required to show effectiveness
 - ▣ “evidence consisting of adequate and well-controlled investigations, including clinical investigations...”
- A&WC can take different forms
 - ▣ Often a randomized double-blind clinical trial with concurrent control (“Phase III”)

Statistical implications of standards

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- “Substantial evidence” usually means:
 - ▣ Statistically significant (one-tailed $\alpha = .025$)
 - ▣ Evidence of clinical benefit
 - ▣ From more than one trial
- There are exceptions
 - ▣ Surrogate endpoints
 - ▣ Single-trial approvals

Additional effectiveness information

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- In addition to approving a product for marketing, FDA approves the content of informational material distributed along with the product
 - ▣ Package insert [PI], prescriber information, ...
- PIs may contain a variety of assertions about effectiveness on different endpoints
 - ▣ Effects need to be clinically significant, statistically significant
 - ▣ Endpoints need to be prospectively defined

Multiple Endpoints in Clinical Trials

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Scott Goldie at 301-796-2055 or (CBER) Office of Communication, Outreach, and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
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Center for Biologics Evaluation and Research (CBER)

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Clinical/Medical

Why we care about multiple testing

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- Multiple testing can increase the Type I error rate associated with the decision to approve a product
 - ▣ Decreases the certainty that approved products work as described
- Multiple testing can increase the probability of false or misleading information appearing in product labeling

Family-wise Type I error rate inflation

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Number of ind. tests	Type I error rate	Number of ind. tests	Type I error rate
1	2.50%	7	16.24%
2	4.94%	8	18.33%
3	7.31%	9	20.38%
4	9.63%	10	22.37%
5	11.89%	20	39.73%
6	14.09%	50	71.80%

Multiple endpoints guidance

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- A collaboration of FDA statistical and clinical experts
- Non-technical language to reach a broad audience
- Extensive discussion among stakeholders to achieve consensus and clarity
 - ▣ Many stakeholders for something like this
- Substantial detail
 - ▣ 50 pages!

Sources of multiplicity in clinical trials

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- Multiple endpoints
- Multiple doses
- Multiple regimens
- Multiple studies
- Multiple timepoints
- Interim analyses
- Multiple analysis methods
- Multiple subgroups
- Analysis populations
- ...

Scope of draft Guidance

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- *Primary* analysis of multiple *primary* and *secondary* endpoints in *adequate and well-controlled trials*
- Focus on multiple clinical parameters, including:
 - Need to evaluate multiple endpoints to establish effectiveness for approval
 - Wish to evaluate multiple endpoints to provide additional effectiveness information
 - Composite endpoints

Largely out of scope

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- Other sources of multiplicity
- Exploratory endpoints
- Supportive or sensitivity analyses
 - ▣ Different tests, different populations, different covariates, different imputation, etc.
- Early-phase trials
- Studies other than clinical trials

When is it necessary to adjust

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- Adjust:
 - ▣ Multiple assertions of treatment benefit based on primary & secondary endpoints
 - ▣ Success criteria are such that trial can demonstrate effectiveness in multiple ways
- Not adjust:
 - ▣ Supportive and sensitivity analyses of the same endpoint in the same population
 - ▣ Descriptive analyses

Overarching recommendations

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- Trials should allow individual conclusions about efficacy with respect to each primary and secondary endpoint tested
 - ▣ Strong familywise error rate control
- Global tests generally inflate the Type I error rate for making conclusions on the individual endpoints
 - ▣ Not recommended
- Try not to have too many endpoints!

Major topics discussed

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- Endpoint families
- Multiple primary endpoints
- Co-primary endpoints
- Composite endpoints
 - ▣ Interpretation
 - ▣ Dissection
- Analytical methods for multiple endpoints

Statistical approaches discussed

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- Bonferroni
- Holm
- Hochberg
- Prospective alpha allocation scheme
- Fixed-sequence
- Modified fixed-sequence
- Truncated Holm for parallel gatekeeping
- Multibranching gatekeeping
- Graphical methods
- Resampling-based procedures

Major public comments

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- Statistical material too detailed / too long
 - ▣ Replace with literature references? Move to appendix?
- Other sources of multiplicity should be discussed
 - ▣ Doses, subgroups, interim analyses
- Is strong control across primary and secondary endpoints always needed?
- Too negative on resampling-based methods
- Harmonize with EMA guidelines

Public suggestions for expansion

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- Multiplicity across trials
- Rare diseases
- Safety endpoints
- Complications with non-inferiority testing
- Platform trials and other innovative designs

My own preoccupations

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- Do we have a coherent decision-making process (approval / labeling)? Do we know how decisions relate to outcomes?
 - ▣ How does strong control of Type I error relate to these?
- What about adjusting confidence intervals?
- What about Bayes?

Next steps

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- Small group meeting to discuss finalization plans
- Stay tuned....

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Thank you!