

99N-0386



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FDA Modernization and FDAMA Implementation- *Selected Topics*

FDA External Stakeholders Meeting
Boston University Medical Center
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Meeting & Performance Timelines

FDA Reviewer Training

Advisory Panels



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Background

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- Representing ~ 250 companies
 - Mostly Small to Medium Size
 - Early stage development to commercialized products
- 15 year history of ensuring that “Biotech” Companies reach full potential



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FDAMA Implementation Process Review

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- MBC supports the FDA in its FDAMA mission to realize the “prompt approval of safe and effective new drugs and other therapies ... so that patients may enjoy the benefits provided by these therapies to treat and prevent illness and disease”



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Meetings and Performance Goals

Unresolved Issues Concerning the Draft Guidance on Formal Meetings with Sponsors/Applicants

I. MBC recommendations on Dispute Resolution

- Sponsor provides corrections to FDA-15 days from receipt of minutes from FDA
- FDA provides response to sponsor-15 days from receipt of corrections from Sponsor



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Meetings and Performance Goals

II. MBC Recommendations on Sponsor Requested Fast Track Meetings

- Meetings scheduling within 14 days of request
- Meetings occur within 30 days of receipt of sponsor's request



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FDA Reviewer Training

I. Model Program Experience and Success for Manufacturing

- MBC/FDA developed Vice President Al Gore's Hammer Award winning Model Program for Pilot Pre-Inspection Approvals



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FDA Reviewer Training

II. Develop Model Program for FDA Reviewers

- Strengthens Science -cutting edge technology presented
- Seminar format
- Presentations by academia and industry
- Proposed “neutral” Massachusetts location:
 - University of Massachusetts Biologics Laboratory
 - previous FDA training accommodations
 - CDC alternative site
- Guidance seminars by FDA to companies
 - how to improve reporting, interactions and discussion with FDA



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Advisory Panels

I. MBC Recommended Harmonization of Policy between Divisions

- CBER-companies are forwarded FDA draft panel documents for review and comments prior to the documents being forwarded to Advisory Panels
- CDER rarely provides such opportunity for review
- CBER's procedure allows interaction, clarification and discussion with the FDA before the Advisory Panel meeting



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Advisory Panels

Role of the Advisory Panel

- 3rd party evaluation mechanism for advice particularly regarding scientific controversies
- Advisory Panels impact a companies:
 - ability to raise research dollars
 - cause 20-30% decrease in stock prices even when the product is recommended for approval



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Advisory Panels

Role of the Advisory Panel (cont.)

- Advisory Panels are being utilized too frequently and as endorsers of the FDA not as 3rd party evaluators
- Recommend FDA move to a rapid approval rather than an Advisory Panel meeting if a company demonstrates safety and efficacy.
- Recommend FDA consider a closed advisory panel meeting vs. public forum.
- Recommend developing a “best practice” for utilization.



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Risk / Benefit: Consumer Education



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Risk/Benefit: Consumer Education

FDA's Plan for Statutory Compliance w/ FDAMA (November 1998) -

Objectives:

- Maximizing the availability and clarity of information for consumers and patients regarding new products,
- Implementing inspections and postmarket monitoring,
- Ensuring FDA's access to scientific and technical expertise



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Risk/Benefit: Consumer Education

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- I. Risk / Benefit Analyses expanded in discussions and Agreements throughout the Development Process
 - Document Agreements which will be the Basis of Safety for Product Approval (as well as Efficacy) as part of Critical Meetings held in a timely manner
 - Summary of Risk Agreements presented at Advisory Committee meeting (if applicable)



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Risk/Benefit: Consumer Education

II. Well-balanced Information as part of Overall Health-care Delivery System

- Enhance and Explore Pilot Programs with Primary Patient Contact Personnel - Physicians and Pharmacists
 - e.g. Pharmacist Education Outreach Program
- Collaboration with other Stakeholders - Media, Consumers, Patient groups



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Risk/Benefit: Consumer Education

III. Expand “Scientifically Sound” Information on New Uses and Findings

- Internet: Two-Way Communication Tool
 - New Approved Uses
 - “Scientifically-Sound” Unapproved Uses
 - Safety Profiles / Updated Safety Information
 - Adverse Events Reporting System



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Risk/Benefit: Consumer Education

IV. Enhance Collaborations with Industry, Other Governmental Agencies, Academia, and Patient Groups

- National Institutes of Health



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Fast Track

Generic Biologics

Pediatric Exclusivity Extensions
for Orphan Biologics



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Fast Track

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- I. An “accelerated approval” under the “fast track” program may be granted if a clinical trial demonstrates an effect on a surrogate endpoint or short-term clinical endpoint that is “reasonably likely to predict clinical benefit.”



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Fast Track

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- Is it possible to describe the quantity and quality of data that demonstrate a sufficient correlation between a surrogate endpoint and the expected clinical outcome to conclude that the former is “reasonably likely” to predict the latter?
 - How can the development and approval of “ultra-orphan” drugs be facilitated, given the limited data with respect to both historical controls and biochemical markers/surrogate endpoints?



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Fast Track

II. FDA's "fast track" guidance document recognizes that short-term clinical endpoints may serve as the basis for an accelerated approval, so that longer-term data may be collected on a post-approval basis.



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Fast Track

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- What steps are FDA taking to ensure that this principle is being applied consistently across Centers, Offices, and Divisions?
 - In cases where a primary surrogate endpoint has been met, how useful is it to show corollary trends in secondary endpoints that measure short-term clinical benefit as a means of increasing the probability that the primary surrogate endpoint is indeed predictive of clinical benefit?



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Generic Biologics

Recombinant proteins:

Whether a product is regulated as a “drug” or “biologic” is determined by reference to a 1991 “Intercenter Agreement” between CDER and CBER allocating jurisdiction between the two based on an apparently simple concept:

- *“A product class is defined as a distinct category of agents recognizable by physical characteristics, source materials or pharmacologic properties.”*



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Generic Biologics

Inconsistencies in Determination

I. Manufacturing method is determinative.

- Polynucleotide products – including products complementary to RNA or DNA sequences – are regulated as drugs if they are chemically synthesized.
- Polynucleotide products are regulated as biologics if they are biologically synthesized.



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Generic Biologics

II. Manufacturing method is irrelevant.

- Hormones and antibiotics are regulated as drugs, regardless of molecular structure or method of synthesis.
- Allergenic products and vaccines are regulated as biologics, regardless of molecular structure or method of synthesis.



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Generic Biologics

III. Products from similar source materials are sometimes regulated differently.

- Human tissue-derived products are regulated as drugs.
- Human blood-derived products are regulated as biologics.
- CBER's historical authority over blood and blood products vs. any evidence that a protein that was extracted from tissue is vastly different from the same protein derived from blood.



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Generic Biologics

IV. General principles do not always have general applicability. Drugs contain subclasses that are regulated as biologics, and vice versa. For example:

- The rule that all hormones (including recombinant proteins) be regulated as drugs was not applied to recombinant erythropoietin (EPO), which is regulated as a biologic.
- The general rule that all non-hormone recombinant proteins be regulated as biologics was not applied to recombinant glucocerebrosidase (GCR).



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Generic Biologics

V. Administrative Convenience

- FDA explicitly reserves the right to transfer responsibility for a product from one Center to the other “for scientific or administrative reasons.”



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Generic Biologics

VI. Whether a product is regulated as a drug or a biologic is irrelevant in evaluating the clinical significance of small variations between molecules.

- CDER may be prepared to use the mere fact that a molecule is regulated as a drug as the basis for characterizing similar-but-not-identical molecules as therapeutically equivalent and substitutable, even when the products have never been evaluated in comparative studies.



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Generic Biologics

VII. The current state of the art does not permit one to predict when minor differences in size, weight, composition, and/or structure will alter the clinical profile of a product, and when it will not, especially when the two products are manufactured by different sponsors using different manufacturing techniques.

- Relatively minor differences in the carbohydrate structures of two otherwise-identical glycoproteins will result in significantly different therapeutic effects.



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Generic Biologics

VIII. In the absence of comparative clinical trials, there are compelling scientific reasons for requiring that two molecules be structurally and functionally identical before concluding that clinical trials performed on the first molecule:

- Can be relied upon to approve the second molecule
- Provide for routine substitution between the two.



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Pediatric Exclusivity Extensions for Orphan Biologics

- I. Orphan drug market exclusivity is available to both “drugs” and “biological products.”
- II. FDA has identified both drugs and biologics as “pediatric study priorities.”
- III. FDAMA’s pediatric study provision – which provides for extensions of orphan drug and other forms of market exclusivity under certain conditions – applies only to “drugs.”



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Pediatric Exclusivity Extensions for Orphan Biologics

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- IV. Pediatric extensions of orphan drug exclusivity to also apply equally to both types of products.
 - V. FDA should support an amendment to FDAMA to accomplish this result.