Biowaiver Aspects from a Biopharmaceutics Perspective: Our role in A/NDA original and post-approval Applications

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CDER Small Business and Industry Assistance

Regulatory Best Practices for Global Access to Medicines, Including Anti-TB Medicines
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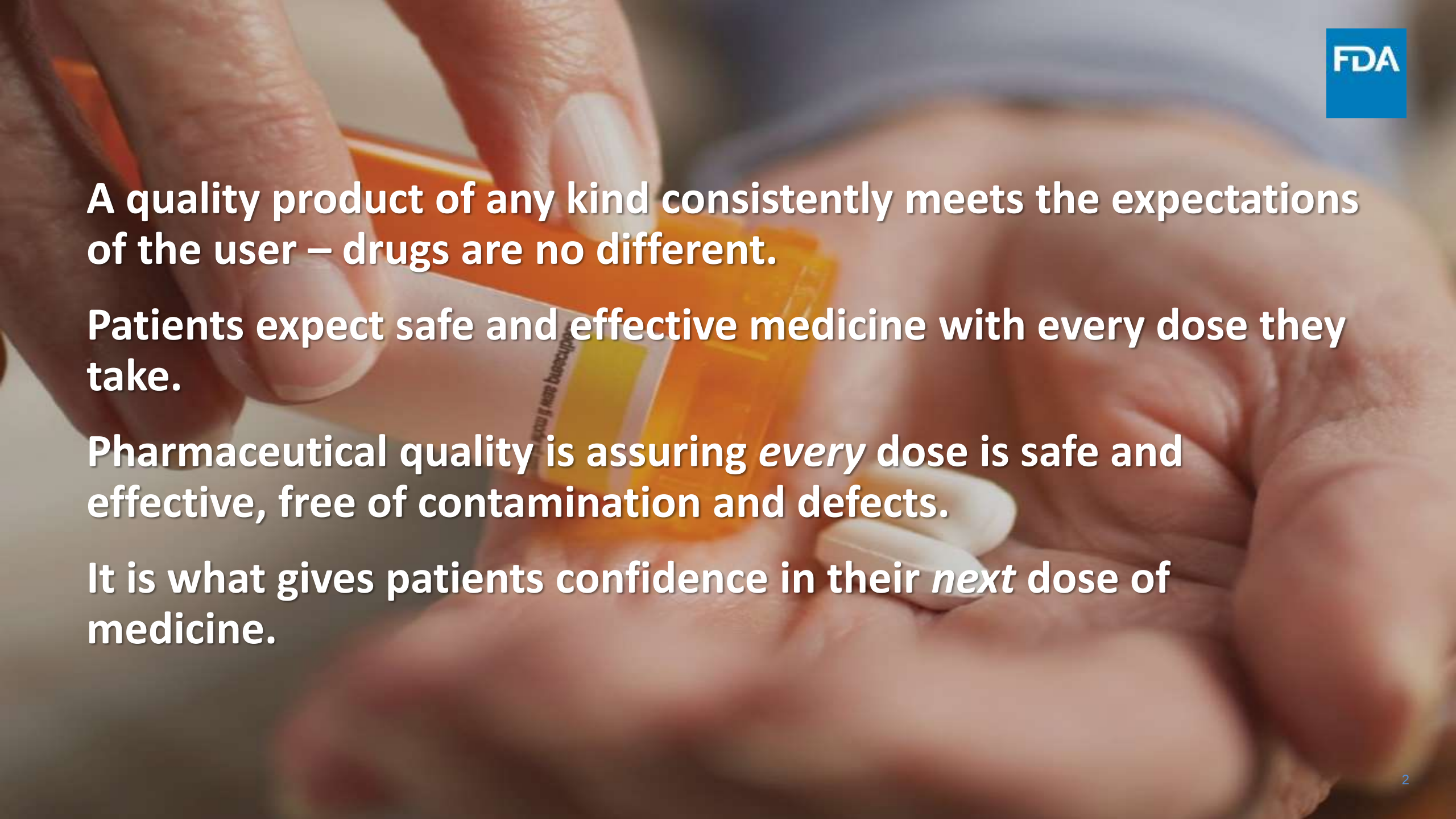

A quality product of any kind consistently meets the expectations of the user – drugs are no different.

Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is assuring *every* dose is safe and effective, free of contamination and defects.

It is what gives patients confidence in their *next* dose of medicine.

Objectives

- To discuss Biopharmaceutics aspects pertaining to biowaiver in original NDA applications
- To discuss Biopharmaceutics aspects of biowaiver as it applies to post-approval NDA/ANDA space
- To present relevant Biopharmaceutics biowaiver Case Studies

Biowaiver Definition: Basis of Biowaiver Submission

- A Biowaiver means that the requirement of conducting in vivo bioavailability and/or bioequivalence (BA/BE) studies can be waived per 21CFR 320.21, any person submitting a full NDA, to the FDA shall include in the application either evidence measuring the in vivo BA/BE of the drug product that is the subject of the applications; or information to permit FDA to waiver the submission of evidence measuring in vivo bioavailability.
- Certain post-approval changes require support from a BA/BE study, unless information to permit FDA to waiver the submission of evidence measuring in vivo BA/BE is provided.

Biowaiver Request

- **Where to find biowaiver requests in A/NDA submissions?**

  Module 1.12.15 Request for Waiver of In Vivo Bioavailability Studies

Biowaiver Request Granted Based on

- **Self-evident BA/BE**
  - **-21 CFR 320.22 (b)**
- **Drug Efficacy Study Implementation (DESI)**
  - **-21 CFR 320.22 (c)**
- **BA/BE demonstrated in vitro in lieu of in vivo data**
  - **-21 CFR 320.22 (d)(2)**
- **IVIVC biowaiver**
  - **-21 CFR 320.22 (d)(3) and 21 CFR 320.24 (b)(1)(ii)**
- **Reformulated product**
  - **-21 CFR 320.22 (d)(4)**
- **Good cause biowaiver**
  - **-21 CFR 320.22 (e)**
- **BCS biowaiver**
  - **-21 CFR 320.24 (b)(6)**

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm

Federal Regulation

21 CFR 320.22

- FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets the defined criteria

21 CFR 320.24(b)

- In vivo and in vitro approaches (as defined), are in descending order of accuracy, sensitivity, and reproducibility, are acceptable for determining the bioavailability or bioequivalence of a drug product.

Biowaiver Requests

Self-evident BA/BE per 21 CFR 320.22 (b)

- Parenteral solution (1)

  -Q1/Q2 same

- Inhalation product (2)

  -Same API and dosage form

- Non-parenteral solution (topical, oral (elixir, syrup, tincture), nasal, or similar other solubilized form etc.)(3)

  -Same API and dosage form

  -No inactive ingredient affects BA of API

Biowaiver Requests

DESI products per 21 CFR 320.22 (c)

- Drug products that were introduced to the market from 1938-1962

  -Kefauver-Harris Drug Control Act (1962) requires all drug products to be ***effective as well as safe***

- DESI program established to classify pre-1962 approved drug products as effective for at least one indication in a DESI notice
- Products with no known or suspected BE problems with a corresponding therapeutic equivalence rating in the “Orange Book”

Biowaiver Requests

BA/BE demonstrated in vitro per 21 CFR 320.22 (d)(2)

- Drug product is in the same dosage form, but in a different strength
- This different strength is proportionally similar in its active and inactive ingredients to the strength of the product for which the same manufacturer has conducted an appropriate in vivo study
- The new strength meets an appropriate in vitro test

Biowaiver Requests

IVIVC biowaiver per 21 CFR 320.22 (d)(3) and 21 CFR 320.24 (b)(1)(ii)

- In vitro (dissolution) method is adequate to act as surrogate for in vivo testing as evident using an IVIVC model
- Biowaivers for SUPAC changes that require BE testing
- Biowaivers for additional strengths

Biowaiver Requests

Reformulated product per 21 CFR 320.22 (d)(4)

- Reformulated product is identical except for different color, flavor, or preservative that does not affect BA
- BA of original product has been measured
- Both products meet an appropriate in vitro test

Biowaiver Requests

BCS biowaiver per 21 CFR 320.24 (b)(6)

- Waive in vivo BA/BE study requirements for IR solid oral dosage forms based on the BCS
- Biowaivers may be granted for IR solid oral dosage forms that are BCS class 1 and class 3

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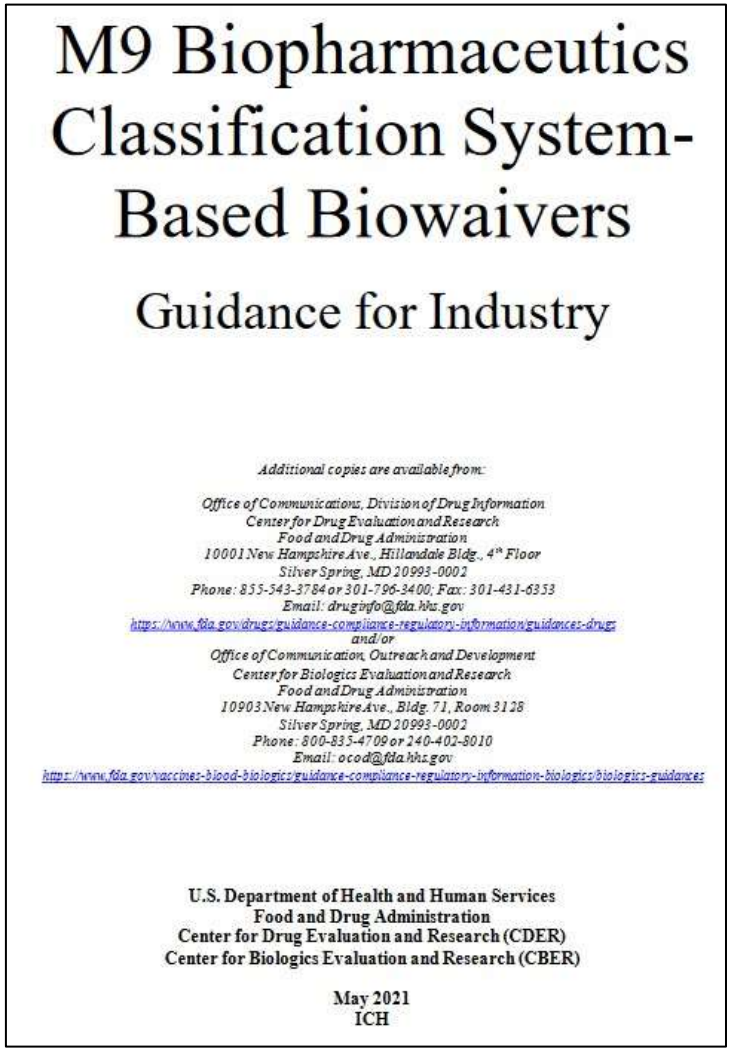


M9 Biopharmaceutics Classification System-Based Biowaivers

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs
and/or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

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

May 2021
ICH

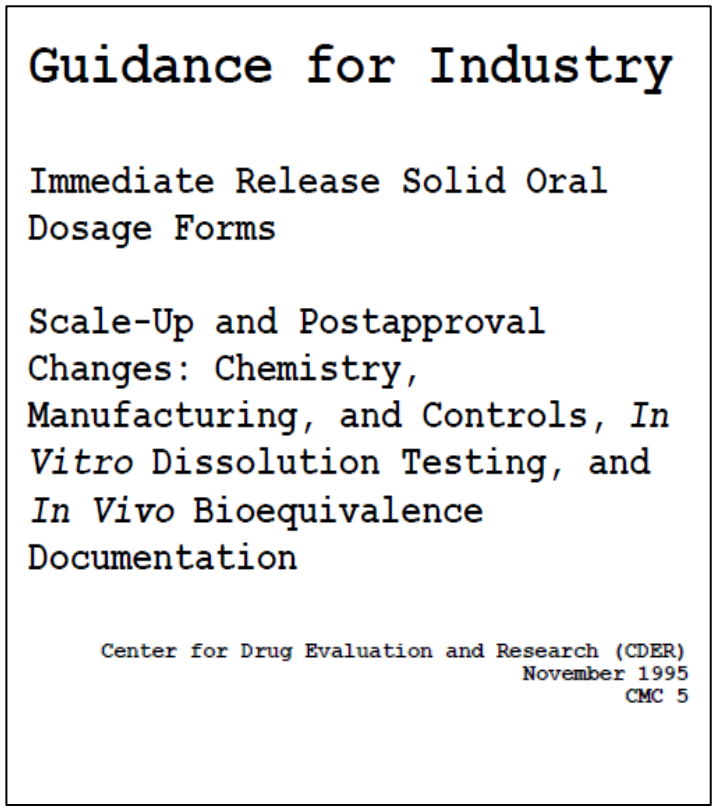
Biowaivers in NDA/ANDA Solid Oral and Semisolid Dosage Forms

- **Formulation development** for a new drug product. Differences in formulation and/or manufacturing between proof-of-principle (Phase II) formulations, pivotal formulations (Phase III) and to be qualified

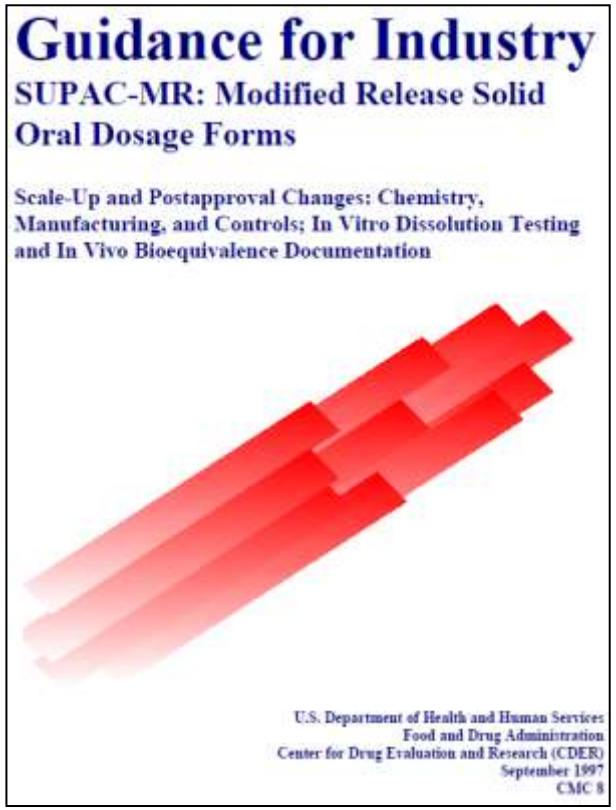
  -NOTE – in vivo bioequivalence study to the ultimate commercial formulation has to be demonstrated (bridging) *–implied biowaiver*

- **Line extensions**, e.g., new strengths or new formulations for a new patient population
- **Post-approval changes**, including changes of the manufacturing formula, in the manufacturing process, in excipients, in manufacturing sites and/or equipment.

Scale-up and Post-Approval Changes (SUPAC)



http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070636.pdf



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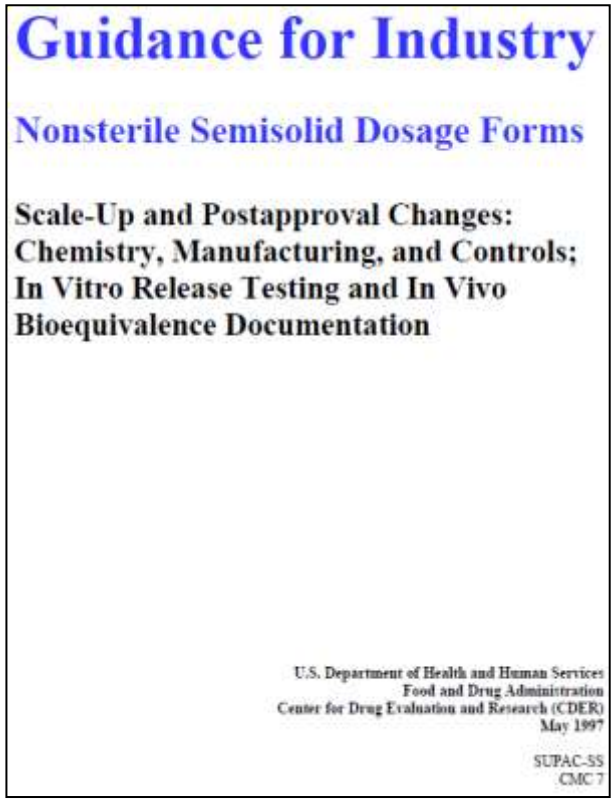


http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070930.pdf

SUPAC for IR and MR Solid Oral Dosage Forms

- SUPAC guidances provide recommendations for approval of the following changes:
  - Components and composition
  - Manufacturing process and equipment
  - Batch size scale-up/-down
  - DP manufacturing site
- Usually 3 levels of change, which determine the need for in vitro testing and/or BE studies

Regulatory Application of Dissolution Testing

- Dissolution similarity testing plays an important role
- It is a critical tool as it is the only product quality/in vitro attribute that relates to the rate and extent of in-vivo drug release.
- Formulation selection during drug product development
- In support of CMC changes as per SUPAC guidance
- Additional strength (s) biowaiver
- Surrogate for BE via biowaiver request based on IVIVC or BCS Class 1/3
- Selection of CMAs/CPPs/CBAs as part of DOE
- Verification of Design Space
- Setting clinically relevant drug product specifications

Dissolution Method Development

- Solubility over physiological pH range
- selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, media pH, assay, sink conditions, use of sinker and enzyme if applicable
- data supporting the selection of the type and amount of surfactant
- The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached

Discriminating Ability

Intentionally manufactured with meaningful variations, (i.e., aberrant formulations and changes to the manufacturing conditions) for the CMAs and CPPs

Dissolution Acceptance Criterion/Criteria

- **Dissolution profile data from pivotal clinical batches**
- **Acceptance criterion based on average in vitro dissolution data (equivalent to USP Level 2 testing (n=12))**
- **IR products: At least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution occurs.**

  -Specification time point should be where Q=80% dissolution occurs (Wider specification ranges based on approved IVIVC model, PBBM, etc)

  -Slow dissolving drug products two time point specification may be considered
- **ER products: Minimum of 3 time points for ER products (early, middle, and late stages of the release profile). The last time point should be where at least 80% of drug is released. If the maximum amount released is less than 80%, the last time point should be the time when the plateau of the release profile has been reached.**

  -Dissolution acceptance criteria ranges mean target value ±10% and >80% for the last specification time-point (Wider specification ranges based on an approved IVIVC model, PBBM, etc).
- **DR products: Delayed release (enteric coated) : acid stage and buffer stage per USP.**

  -Acid Stage: No individual tablet exceeds 10% dissolved at 2 hours.

  -Buffer Stage-IR: Q=80% dissolution/release or the plateau of drug dissolved is reached

F2 Similarity Factor

$$f_2 = 50 \bullet \log \{[1+(1/n)\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

Where n is the number of time points, R_t is the dissolution value of the reference (prechange) batch at time t, and T_t is the dissolution value of the test (postchange) batch at time t

- 12 units
- 3- 4 or more dissolution points
- Time points should be the same (e.g. 15, 30, 45 and 60 minutes)
- Reference batch should be most recently manufactured prechange product
- Only one measurement should be considered after 85% dissolution of both products
- The %CV at the earlier time points (e.g., 15 minutes) is not more than 20% and at other time points is not more than 10%
- Dissolution measurements should be made under same conditions and the dissolution profiles should have the same time points

Case Study 1

- **Fixed dose combination of higher strength is the approved strength as NDA.**
- **Waiver of in vivo BA/BE studies for the pediatric strength of fixed-dose combination tablet per 21CFR 320.22(d)(2) based on**

  -Same dosage form

  -Formulation proportional similarity

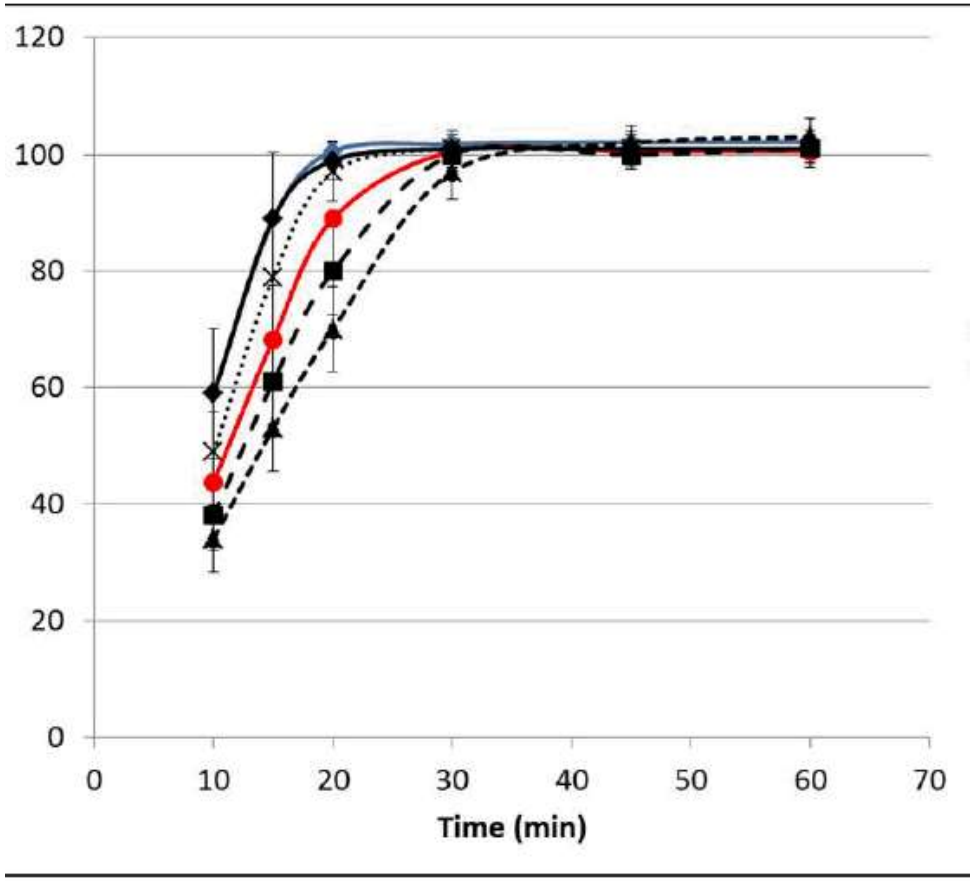
  -Comparable in vitro dissolution profile relative to the original and current version of the reference adult strength FDC tablet.

Case Study 2

BACKGROUD: Plans to develop 5 mg and 10 mg IR tablets as a weight multiple of the 15 mg, 20 mg, 30 mg and 40 mg tablets (proportionally similar in composition). Given this approach and based on previously provided data on the 15 mg, 20 mg, 30 mg and 40 mg tablets, the Applicant concluded in vitro dissolution and stability data would support review and approval of these lower dose strengths, without additional clinical data

CASE: If *f2* testing fails to justify/support the approval of these strengths how can the biowaiver be supported

Case Study 2



Lack of similarity is demonstrated between lower and higher strengths.

	AUC0-last	AUC0-inf	Cmax
4 x 5 mg (n=24) vs 1 x 20 mg (n=23)	96.13% (90.65%-101.93%)	96.13% (90.53%-102.08%)	106.83% (99.14-115.12%)
2 x 10 mg (n=35) vs 1 x 20 mg (n=35)	95.71% (91.54%-100.06%)	96.65% (92.23%-101.29%)	102.28% (94.97%-110.15%)

- CONCLUSION: A biowaiver was **NOT** granted. The dissolution data and additional bioequivalence study provided supported the approval of the 5 and 10 mg strengths.

Acknowledgements

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FDA U.S. FOOD & DRUG ADMINISTRATION

Thank you !