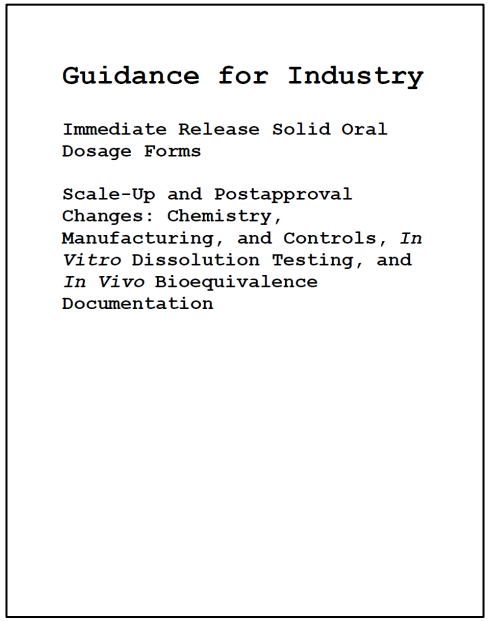
Scale-Up and Postapproval Changes (SUPAC)

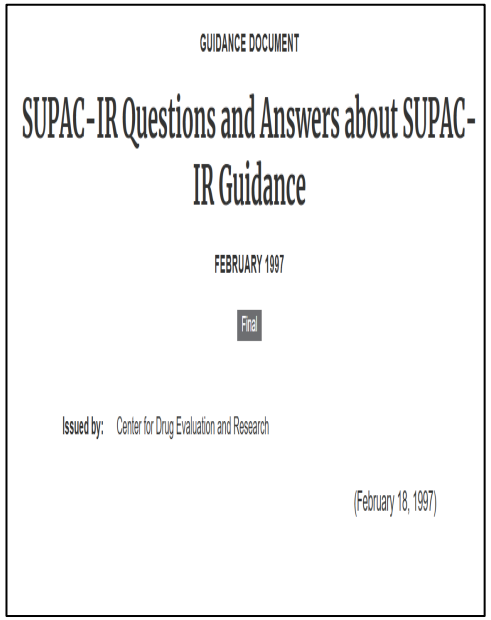
CAPT. Mahesh Ramanadham, Pharm.D., MBA
Deputy Director, Office of Regulatory Practice for Pharmaceutical Quality
FDA/CDER/OPQ


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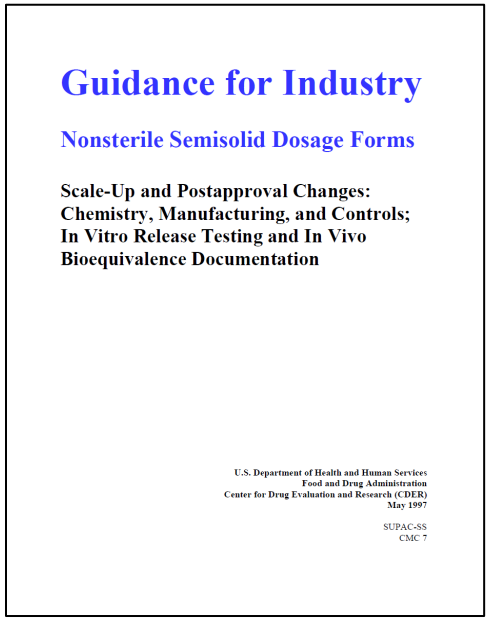
Background



SUPAC-IR
Nov 1995



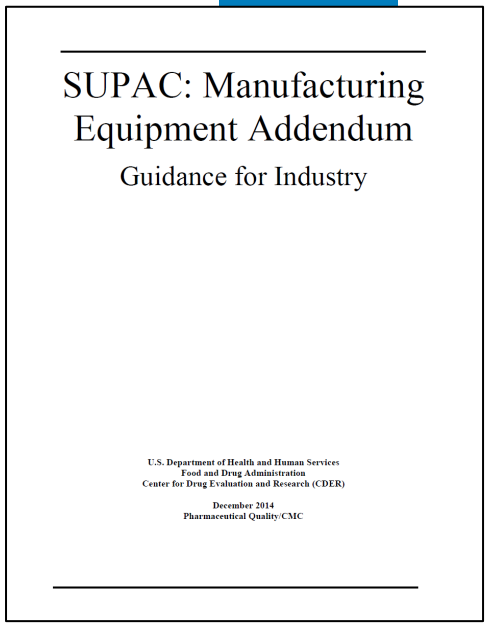
SUPAC-IR Q&A
Feb 1997



SUPAC-SS
May 1997



SUPAC-MR
Oct 1997



SUPAC-MEA
Dec 2014

- SUPAC = Scale-up and Postapproval Changes
- SUPAC guidances developed based on FDA sponsored research and workshops to better understand postapproval CMC changes and their effects on the identity, strength, quality, purity or potency of a drug product as they may relate to the safety or effectiveness of the product
- SUPAC guidances describe a risk-based approach to postapproval CMC changes

Scope of SUPAC Guidances

- **Applies to:** NDA and ANDAs for immediate release & modified release oral dosage forms, and semi-solid dosage forms

- **Postapproval changes include:** (1) components or composition; (2) manufacturing site; (3) manufacturing scale-up/scale down; (4) manufacturing process and equipment

- **Recommendations include:** (1) levels of change; (2) CMC tests for each level of change (including stability); (3) in vitro dissolution tests and/or in vivo bioequivalence tests for each level of change; (4) documentation that should be submitted to support the change

A lot has changed since the ‘90s!



Postapproval Changes Landscape

- **Food and Drug Administration Modernization Act (FDAMA)-1997 (final rule implemented in 2004):**
  - Codified the risk-based approach described in the SUPAC guidances
  - Requires applicants assess the effects of CMC changes on the identity, strength, quality, purity and potency of a drug product as they relate to the safety and effectiveness of the product and categorize changes based on risk (major, moderate, minor)
  - Preamble to the final rule acknowledges scientific thinking and manufacturing technology evolves with time and FDA may revise its thinking on category of change (e.g., publishing of guidance, updating 314 regs)

- **Generally Applicable to ANDA/NDA**
  - Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA (2022)
  - CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports (2014)
  - Changes to an Approved NDA or ANDA; Specifications – Use of Enforcement Discretion for Compendial Changes (2004)
  - Changes to an Approved NDA or ANDA (2004) + Questions and Answers (2001)
  - PAC-ATLS: Postapproval Changes - Analytical Testing Laboratory Sites (1998)

Postapproval Changes Landscape

- **International Conference on Harmonisation:**
  - ICH Q14: Q14 Analytical Procedure Development (2024)
  - ICH Q9 (R1): Quality Risk Management (2023)
  - ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management: Guidance for Industry (2021) + Annexes (2021)

ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

- ICH Q12 provides a framework to facilitate the management of postapproval CMC changes in a more predictable and efficient manner
- Applicants can reduce the number of CMC changes that require a postapproval submission by using ICH Q12 tools
- This benefit increases with stronger scientific development, risk management, and quality systems throughout the product lifecycle
  - Weaker: likely more established conditions
  - Stronger: opportunity for fewer established conditions
- Applicant's use of ICH Q12 is voluntary

APPLICATION TYPE	ORIGINAL	SUPPLEMENT	APPROVED
Biologic License Application	6	21	17
New Drug Application	8	7	13
Abbreviated New Drug Application	0	0	0
Total	14	28	30

Table includes applications from FDA's established conditions pilot (2019) and post implementation (2021 – present)

SUPAC Federal Register Notice (FRN)

- Federal Register Notice published on March 3, 2026: *Recommendations on Scale-Up and Postapproval Changes Guidances for Industry; Request for Comments*
  - Soliciting comments on 5 current SUPAC guidance documents
  - Acknowledge the changes in thinking and subsequent guidances (e.g., ICH) with superseding or conflicting recommendations
  - Seeking comments from industry on potentially updating the SUPAC guidances to improve utility and effectiveness

- Comments sought regarding:
  - Whether recommendations in SUPAC guidances are still helpful and meaningful
  - Challenges in interpreting or applying current recommendations
  - How FDA can provide clarity on the recommendations in the SUPAC guidances
  - If there are any new topics that should be added to the SUPAC guidances