

FDA's Revised Proposal on Site-Specific Stability Data

General Issues and Approaches

Q1A deals adequately with changes in the manufacture of the drug substance and drug product between pivotal clinical trial batches and the to be marketed dose form, with the exception of site changes involving manufacture of the drug substance and drug product at pilot facilities and the proposed site of commercial manufacturing. The SSS approach is designed to recommend additional stability data based on a three tiered, risk-based system that is in accord with the statutory language expressed in section 116 of the Food and Drug Administration Modernization Act. The approach involves the submission of additional stability data, as well as the timing of the receipt of this information by the Center.

I. Drug Substance

A. Additional information

For synthetic drug substances, up to, but not including, the final intermediate, generally no additional stability data are recommended if the impurity profile does not change. For site changes involving the final intermediate and/or the drug substance, the recommendation for additional information may be similar to those in BACPACII Site specific stability data are recommended for complex drug substances.

B. Timing

Timing of receipt of additional information (i.e., prior to NDA filing, during NDA review, or post-approval of the NDA) relates to the potential for the change to the new site to impact on the identity, strength, quality, purity, and potency of the drug substance as they may relate to the safety and effectiveness of the drug product. Generally, these risk-based concerns will be less of an issue for synthetic drug substances when compared to drug products.

II Drug Product

A. Additional information

The SUPAC recommendations for site change may be generally applicable, including those that relate to manufacturing experience. Site specific stability data are recommended for non-SUPAC dosage forms.

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Table 1: Timing of Site-Specific Stability Data for an Original Application

	Potential to have an adverse effect on the drug substance/product stability due to site-transfer		
	Major	Moderate	Minor
When the site-specific stability data will be needed	At submission	Midpoint in the review cycle	Post-approval in the Annual Report* (NDAs/ANDAs)

*Applies if the commercial facility is approvable with the application.

Table 2: Site-Specific Stability Data for a Drug Substance for an Original Application

	Potential to have an adverse effect on the drug substance stability due to site-transfer		
	Major	Moderate	Minor
Examples	Drug substance whose polymorphic form or particle size is critical to the performance of the drug product.	Drug substances susceptible to manufacturing conditions, technology or site transfer (e.g. biotechnology/ biological products; environmentally sensitive substances).	All others
Amount of SSS Data	3 months of accelerated and long-term data on 1 batch, if sufficient primary data are available; or on 3 batches, if sufficient primary data are not available; plus the standard stability commitment.	3 months of accelerated and long-term data on 1 batch, if sufficient primary data are available; or on 3 batches, if sufficient primary data are not available; plus the standard stability commitment.	The standard stability commitment

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Table 3: Site-Specific Stability Data for a Drug Product for an Original Application

		Potential to have an adverse effect on the drug product stability due to site-transfer		
		Major	Moderate	Minor
Examples		<ul style="list-style-type: none"> • Modified release solid oral dosage forms • Sterile lyophilized powders • Liposomal formulations • Meter-dosed inhalers • Dry-powder inhalers • Transdermal patches 	<ul style="list-style-type: none"> • IR solid oral dosage forms where the Drug substance has low solubility/low permeability or low solubility/high permeability. • Suspensions, semisolids, sterile solutions (including nasal, ophthalmic, topical solutions), sterile powders • Drug Products containing drug substances potentially susceptible to manufacturing conditions (e.g. biotechnology/biological products, environmentally sensitive drug substances). 	<ul style="list-style-type: none"> • IR solid oral dosage forms -- Drug substance has high solubility/low permeability or high solubility/high permeability • Non-sterile solutions, powders for oral solution or suspension
Amount of SSS Data	NDA	3 months of accelerated (from a 6-months study) and long-term data on 3 batches, if sufficient primary data are available; or 6 months of accelerated and 12 months of long-term data on 3 batches, if sufficient primary data are not available; plus the standard stability commitment.	3 months of accelerated (from a 6-months study) and long-term data on 1 batch, if sufficient primary data are available; or on 3 batches, if sufficient primary data are not available; plus the standard stability commitment.	The standard stability commitment
	ANDA	3 months of accelerated and long-term data on 3 batches; plus the standard stability commitment.	3 months of accelerated and long-term data on 1 batch; plus the standard stability commitment.	The standard stability commitment

Site-Specific Stability Expert Panel
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Holiday Inn Bethesda

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