

Food and Drug Administration
Center for Drug Evaluation and Research
Public Meeting
Site Specific Stability Data for Drug and Biologic Applications

March 31, 1999
Holiday Inn Bethesda
8120 Wisconsin Avenue, Bethesda, MD

9:00- 9:05	Call to Order/Welcome	Kimberly Topper
9:05 - 9:15	Overview and Objectives	Roger Williams, M.D.
9:15- 9:25	Scientific Issues and Examples	Robert Seevers, Ph.D.
9:25 - 9:45	Academic Viewpoint	Stephen Byrn, Ph.D.
9:45 - 10:05	Industry Viewpoint	
	Consumer Healthcare Products Association	William Bradley
	Generic Trade Associations	Robert Kasubick, Ph.D.
	Generic Pharmaceutical Industry Association National Association of Pharmaceutical Manufacturers National Pharmaceutical Alliance	
	Health Industry Manufacturers Association	Karen Malik
	Pharmaceutical Research and Manufacturers of America	Scott Reynolds, Ph.D.
10:05 - 10:15	Break	
10:15 - Noon	Presentations by the public	
	Scheduled Speakers	
Noon - 12:20	Break	
12:20- 2:00	Open Microphone/ Discussion	
2:00	Adjourn	

98D-0362

SUP 1

FDA's Revised Proposal on Site-Specific Stability Data

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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Revised Proposal on Site-Specific Stability Data

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	NDAs	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
	ANDAs	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

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.

II. Drug Product (Cont.)

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 product as they may relate to the safety and effectiveness of the drug product.

III. Alternative approaches

Alternative approaches may be justified based on a high degree of certainty that the change of environment would have little or no effect on the drug substance or drug product stability and that process validation and technology transfer adequately address any site change concerns. Further, medical need and/or other factors (e.g., cost) may allow for a reduction in the additional stability data recommended and /or a change in the timing of the filing.

IV. Further research

Further retrospective (e.g., data mining) or prospective (e.g., conducted at PQRI or elsewhere) research might allow for an alteration in these recommendations.

Site-Specific Stability Expert Panel
March 31, 1999
Holiday Inn Bethesda

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**Site-Specific Stability Expert Panel
March 31, 1999
Holiday Inn Bethesda**

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Site-Specific Stability Meeting
March 31, 1999
Open Public Hearing Speakers

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Hoechst Marion Roussel,
Drug Regulatory Affairs

James E. Curley
Team Leader,
Analytical Resources Group,
Quality Operations
Pfizer, Inc.,

Robert A. Jerussi
Jerussi Consulting, Inc,

Tony Amann
Vice President
Eon Laboratories Manufacturing, Inc.,

Dr. Patricia Tway
Merck & Co., Inc.

Tobias Massa,
Director, Global Regulatory Affairs
Eli Lilly and Co.

Mark D. VanArendonk
Pharmacia Upjohn

Taylor Burtis
Genentech, Inc.

Robin Roman
Director, Pharmaceutical Development
SmithKline Beecham Pharmaceuticals

**DOCUMENTS CONNECTED WITH THIS MEETING
MAY BE REQUESTED FROM THE
FREEDOM OF INFORMATION (FOI) OFFICE**

A written request specifying date of the meeting, name of committee, and a description of the document(s) requested, may be mailed to:

**Food and Drug Administration
Freedom of Information Staff
HFI-35, Room 12A-16
5600 Fishers Lane
Rockville, Maryland 20857
(301) 827-6500**

**or Faxed to:
(301) 443-1719/1726**

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one meeting per CD - PDF or WordPerfect format
- Diskettes at \$4.50 each,
one diskette per meeting day - WordPerfect format
- or printed copy at \$.10 per page.

You may purchase the transcripts directly from the transcribing company.

Miller Reporting Company is transcribing this meeting. Phone: 202-546-6666

SUMMARY MINUTES will be available from FOI approximately 90 days after the meeting. Please wait until this time period has elapsed before you place your order. Allow time for the minutes to be written, edited, approved, and photocopied for distribution. You may phone the Advisors and Consultants Staff at (301) 827-7001 for status of minutes.

INVOICES are sent out monthly by the FOI Staff. If requested, FOI will inform you of fees in advance.

Food and Drug Administration/Center for Drug Evaluation and Research
Public Meeting
Site Specific Stability Data for Drug and Biologic Applications
Holiday Inn Bethesda
March 31, 1999

Overview and Objectives

ROGER L. WILLIAMS, M.D.
DEPUTY CENTER DIRECTOR FOR PHARMACEUTICAL SCIENCE
CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

**Food and Drug Administration
Center for Drug Evaluation and Research
Public Meeting
Site Specific Stability Data for Drug and Biologic Applications**

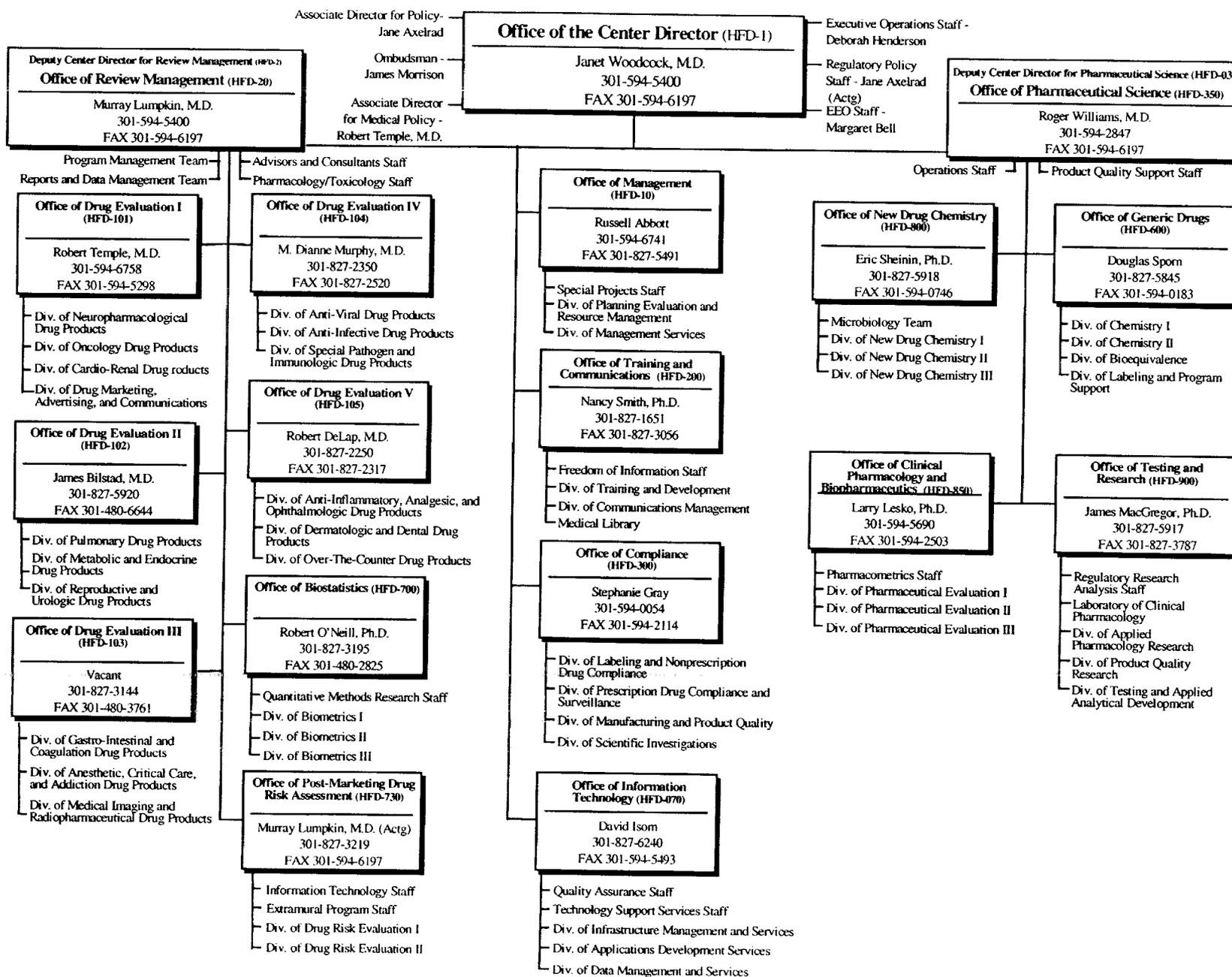
March 31, 1999

**Holiday Inn Bethesda
8120 Wisconsin Avenue, Bethesda, MD**

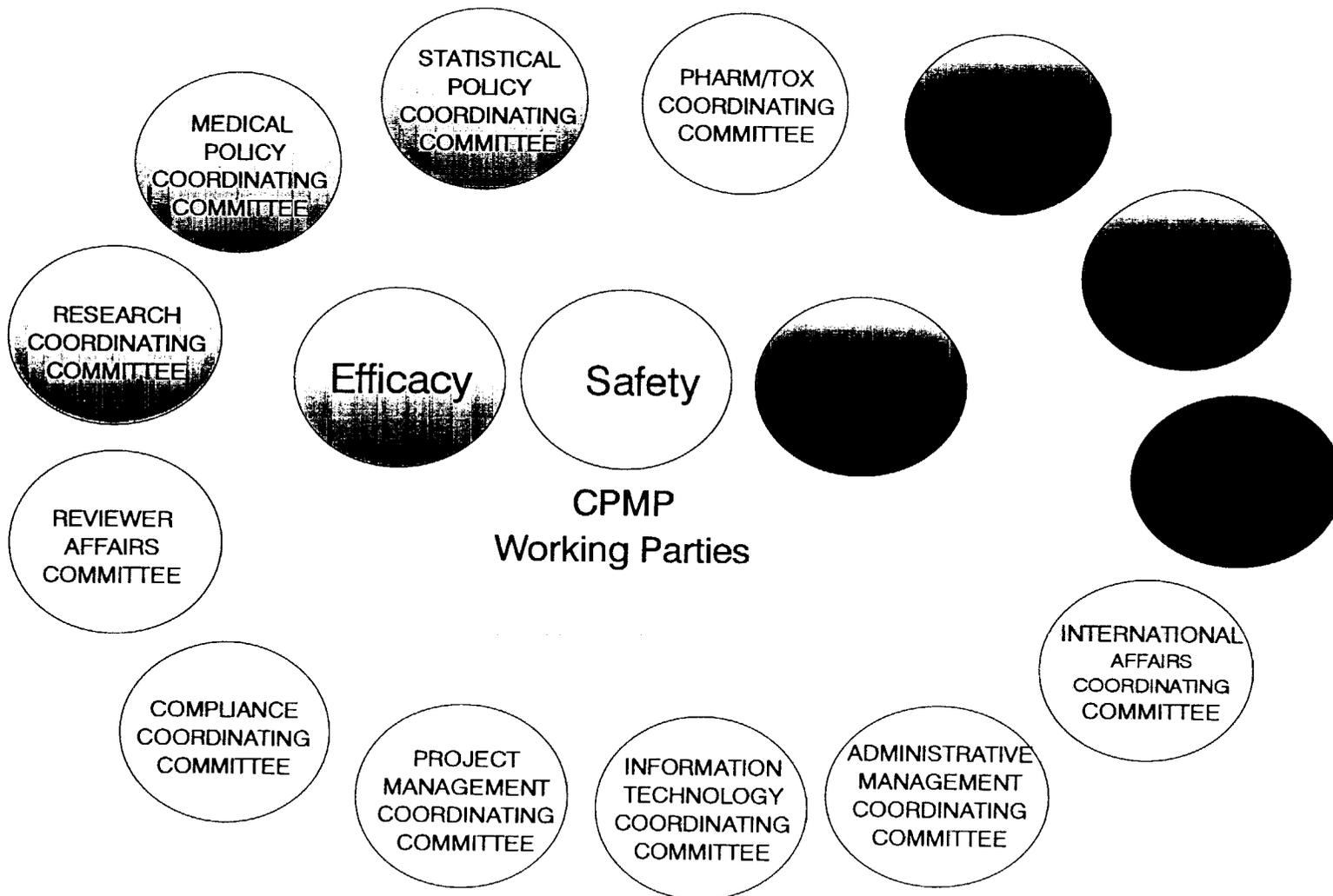
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CENTER FOR DRUG EVALUATION AND RESEARCH

AS OF: 01/15/99



CDER COORDINATING COMMITTEES



Pre-Approval

Drug Substance

General
 Impurities: Q3A, D-ANDA/NDA
 Residual Solvents: Q3C
 Tests and Specifications: Q6A
Chiral Information (May 1992 Update)

Drug Product

General
 Tests and Specifications (Q6A)
 Degradants: Q3B, D-ANDA/NDA
 Residual Solvents: Q3C
 Container Closure Systems
 Sterilization Process Validation
 Oral Inhalation/Nasal (MDI/DPI, Other)
 Ophthalmic/Otic
 Topicals/SS

General

Methods Validation: Q2A, Q2B, D
 DMFs
 Environmental Assessments
 Stability Q1A, Q1B, Q1C, D
 CMC IND Phase 2/3
 CMC IND Formal Meetings
 Proprietary Drug Names

CMC CC

314.70

Post-Approval

General
 Guidance

BACPAC I and II

SUPAC: IR/MEA, MR/MEA

PAC-SAS

PAC-OI/N

PAC-OO

PAC-SS/MEA

PAC-Analytical Testing Labs

CDS CC

314.70
 (g)

Changes
 Guidances

1) Biologicals
 2) Specified
 Biotech/Other

PAC by CDS*

Comparability Protocol
 (April 96)

Complex Drug Substance

rDNA Derived Cell Metabolites
 Synthetic Peptides
 rDNA Proteins (g/ng)
 Natural Proteins (g/ng)
 Conjugated Estrogens
 Botanicals
 rDNA Reagents
 Complex Excipients

*May be part of the guidance on individual topics or drugs.

Stability Document

- NDA rewrite June 1985
- Guideline for submitting documentation for the Stability of Human Drugs and Biologics Feb 1987
- Redraft of FDA Stability Guidance Began 1992
- ICH Q1A Sept 1994
- ICH Q1B May 1997
- ICH Q1C Nov 1996
- Guidance for Industry; Stability Testing of Drug Substances and Drug Products June 1998
- Meeting with Industry on Site Specific Stability July 1998
- Comment period ended Dec 1998

FDA's Revised Proposal on Site-Specific Stability Data

General Issues and Approaches

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IV. Further research

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Roger Williams, M.D.

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Representatives

Academic

Garnet Peck
Steve Byrn
Chris Rhodes
Larry Augsberger
Leon Lachman
Fred Regnier

Industry

Bill Bradley
Robert Kasubick
Scott Reynolds
Karen Malik

FDA

Robert Seevers/CDER
Ken Furnkranz/CDER
Eric Sheinin./CDER
Rebecca Devine/CBER

Site-Specific Stability: Scientific Issues and Examples
Robert H. Seevers, Ph.D.

A Brief History

- Current Thinking Presented in 6/98 Draft
- July 21, 1998 Meeting on SSS
- Stability Guidance Comments on SSS
- 2/3/99 Pre-meeting: Academic Experts/SSS
- Proposed Modifications to SSS Guidance
- 3/31/99 Open Meeting on SSS

Comment on Draft Guidance

- 60+ Entities (Individuals, Groups, Firms, Trade Organizations) provided comments
- 575+ pages of comments
- 2,000 - 3000 individual comments
- All Aspects of Guidance covered.

SSS Comments

- 25 Entities commented on SSS
 - Regulatory (8)
 - Scientific (13)
 - Logistical / Economic (12)
 - Technical (2)

Scientific Comments

- SSS not based on scientific logic
- Process Validation is all that is needed
- Stability is intrinsic to the drug product
- Site Change is less critical than Scale-up (which requires no stability data)
- Inconsistencies; NDAs vs. ANDAs
- SSS not applicable to D.S.

Regulatory Comments

- Contrary to ICH
- SSS is inconsistent with FDAMA
- ICH allows pilot batches to support a "conservative" Expiration Date, therefore, SSS is not necessary

Site-Specific Stability: Scientific Issues and Examples

Robert H. Seevers, Ph.D.

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Logistic/Economic/Technical

- SSS at submission of NDA burdensome
- Complex Dosage Forms: 3 batches excessive
- "Intrinsically Unstable" needs definition
- Definition of "Complex Dosage Forms" needs clarification

Example 1

- IR tablets with 24 m expiry at original site
- 3 tech transfer lots fail or have borderline assay at 15 m
- Expiry reduced to 12 m at new site
- Biostudy shows material from new site is not bioequivalent

Example 2

- IND capsule packed in non-US facility
- NDA drug product packed in US facility
- Delamination of blister packaging: stability compromised
- Cause attributed to heat sealing at US facility

Example 3

- Injectable combination drug with epinephrine
- At new site, firm adds 8%, then 11% epinephrine overage
- Stability failures trigger reduction in expiration dating: 36 m to 24 m, then 18 m

Example 4

- Pre-approval site change for IR tablets: hygroscopic
- Supplement for manufacturing sites in PR and PA
- Stability testing shows that product mfg in PR has significantly shorter projected expiry
- PR site withdrawn

Example 5

- Site Renovation
- Tablets in blister package
- Satisfactory data on several lots
 - 6 m acc/60 m LT
- Mfg site renovated
- Several lots made after renovation fail dissolution at 2 m acc test station

Example 6

- Inhalation solution in Blow-Fill-Seal ampoules
- Met all specifications at release
- Stability samples darkened over time
- Problem traced to a change in one of the head fillers on the ampoule fill line

Example 7

- Antibiotic drug substance
- Assay failures on stability
- Problem traced to stainless steel solvent holding tank
- Tank leach heavy metals that catalyzed degradation

Example 8

- New facility had several lots recalled for sub-potency and low preservative
- Investigation showed that active and preservatives adsorbing to PVC tubing
- Problem previously detected at former mfg site
- New site was never apprised of the problem

Example 9

- Manufacturing suspended at original site after polymorph detected
- Manufacturing transferred to contract facility
- In a few years polymorph also detected during stability testing of product manufactured by contractor

Example 10

- Enteric coated tablet: site transfer from pilot to production
- Pilot stability studies established 18 m expiration dating period
- Production lot failed dissolution at 3 m

FDA SSS Approach

- Site-specific stability data are needed and are being generated now; the key question is the timing of the submission of these data
- Three-tiered risk-based system
 - assess potential to have an adverse effect on the drug substance or drug product stability due to site transfer

SUMMARY PREMEETING OF ACADEMIC EXPERTS SITE SPECIFIC STABILITY

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F. REGNIER

G. PECK

C. RHODES

L. LACHMAN

L. AUGSBARGER

Presented
March 31, 1999

#2

Stephen Byrn, Ph.D.

QUESTIONS ADDRESSED

- ① Can/does a site-transfer affect the quality and/or performance of a drug product? (yes, no, possibly) Why or why not?
- ② If the answer to #1 is yes or possibly, what are the factors that can/do potentially affect the quality and or performance of a drug product?

QUESTIONS ADDRESSED

- ③ If the answer to #1 is yes or possibly how can a firm demonstrate sameness of a drug product before and after site-transfer? Is it through:
- ⇒ technology study?
 - ⇒ process validation of production batches?
 - ⇒ release testing of site-specific batches?
 - ⇒ stability testing of site-specific batches?
 - ⇒ in-vivo or in-vitro bioequivalence study?
 - ⇒ a combination of some or all of the above?

IF ONE OF THE ANSWERS TO 3 IS THROUGH STABILITY TESTING OF SITE-SPECIFIC BATCHES

- What are the circumstances under which stability studies can be waived or deemed unnecessary prior to the approval or marketing of the drug product?

QUESTION 2 - FACTORS THAT CAN/DO POTENTIALLY AFFECT THE QUALITY OF A DRUG PRODUCT

- Stability includes both chemical and physical stability
- Examples
- Change in environmental conditions
 - » relative humidity
 - » seeds
 - » materials handling/processing
- Other changes not controlled in original validation because changes were not foreseen
- Statements at BACPAC meeting that the same drug substance performs differently on use-tests
- Cases where drug substance changes upon formulation -
in situ salt formation

What are the circumstances under which stability studies can be waived or deemed unnecessary prior to the approval or marketing of the drug product?

Highly soluble/ Low permeability drug known to be stable (both physically and chemically) under stress

HIMA Presentation

FDA Meeting on Site Specific Stability

March 31, 1991

HIMA Presentation - Site Specific Stability

- ◆ Supports the PhRMA position
- ◆ Technical data support the manufacturing process developed and the expiration dating established
- ◆ Technology transfer and process validation
 - demonstrate conformance to GMP
 - support the reproducibility and robustness of the process
 - provide assurance that product will meet established specifications

HIMA Presentation - Site Specific Stability

- ◆ Specifications are defined to ensure product acceptability throughout the dating period
- ◆ No technical basis to support that product stability will be affected by a manufacturing site change, provided the process is shown to be equivalent
- ◆ Experience base has not identified any difference in product stability due to manufacturing site change alone

PhRMA Presentation to the FDA
Public Meeting on Site Stability
Holiday Inn, Bethesda

Scott Reynolds, Ph.D.
Merck Research Laboratories

March 31, 1999

Define the Issue

- What is the best marker for successful Scale-up and technology transfer?
- Evidence of successful technology transfer
 - Demonstration of a reproducible and robust process
 - Clear bridge to the product used in clinical trials
- Process validation is the accepted marker for successful technology transfer

Validation Definition

Process validation is establishing documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics.

Guidelines on general principles of process validation,
Division of manufacturing and product quality (HFN-320)
Center for drugs and biologics (FDA), rockville, MD.
(May 1987)

Site Stability - Limited Utility

- 3 month accelerated site stability only confirms 1st data point (or only the early portion) on stability curve
 - Is not a surrogate to demonstrate effective process scale-up or process transfer
-
-
-

Stability - Examined Extensively During Development

- Identify mechanism and rate of degradation
- Predict degradate levels at expiry
 - Triggers safety qualification
- Evaluate and define packaging/storage conditions
- Set specifications for product acceptability
 - At release and at control
- Results used in NDA evaluation by FDA

Process Development

- Continuum of process development
 - Laboratory \Rightarrow pilot plant \Rightarrow manufacturing
 - Identification of appropriate formulation composition, processing conditions and environmental control parameters during development
-
-

Process Validation Begins in Development

- Establish processing equipment and conditions for a robust process
- Identify critical quality attributes of intermediates and final product

Process Validation

Begins in Development (cont'd)

- Identify and define critical process parameters
 - In process controls
 - Regulatory
 - Internal
- Form basis of scale-up plans and process validation exercise

Deliverables - Process Validation

- Demonstrate reproducibility of process and equivalence of product on scale-up
 - Consistency of critical process parameters and quality attributes
- In process controls ensure control of unit operations in each batch

Manufacturing Site

- Site specific GMP issues are covered in detail at the manufacturing plant
- Facilities validation - GMP issue
 - SOPs
 - Suppliers
 - Water and utilities
 - Environmental conditions
- Equipment qualification - GMP issue

Process Development - Link to Manufacturing Site

- Implement environmental controls at manufacturing site
- Select parameters for process validation
 - Product specifications and in process controls
- Success of scale-up and technology transfer judged by consistency of these quality attributes during full-scale demonstration and validation runs

Stability Is Confirmed in the Final Manufacturing Plant

- Firm is obligated to meet stability requirements (first three manufacturing batches) after launch or risk recall
- Release testing ensures every batch of product meets pre-determined specifications
- Annual stability testing monitors product quality on an ongoing basis

Summary

- Successful technology transfer requires:
 - Thorough process development experience
 - Design and operation of manufacturing plant to conform with GMPs
 - Demonstration of process robustness through process validation in the manufacturing plant
- The value of Site Stability has not been demonstrated and is not the best method to provide assurance of successful technology transfer

THE GENERIC INDUSTRY'S CONTRIBUTION TO THE SITE-SPECIFIC STABILITY DEBATE

March 31, 1999

The following two charts give some examples of multiple generic approvals of solid oral dosage forms for the same drug products. The test or pilot batches were all made at different sites (SUPAC-IR level 3) and thus the three month accelerated data on one batch was obtained on these products. Certainly, they did not all contain the same formulations, manufacturing procedures or NDS source. The speaker has not checked to see if each approved drug made it to the market place but many of them did.

The FDA recall list has been checked from 1992 to February, 1999 for recalls of any of the listed products for stability reasons. Only one was found for the same firm for cimetidine tablets, 800 mg which failed dissolution before the expiration date.

Note that one drug, diclofenac, is a modified release product. Another drug not listed is diltiazem hydrochloride sustained release capsules for which there are at least two generic approvals. A search indicated three recalls due to dissolution failures for products that were either distributors or branded products.

Conclusions: FDA has the data to verify whether or not immediate release solid oral dosage form products need stability data re site transfer and should gather it. The Agency should also look at modified release products which may also meet this category.

**Robert A. Jerussi
Jerussi Consulting, Inc.**

SAME DRUG PRODUCT MANUFACTURED AT DIFFERENT SITES

PQRI - DRUG PRODUCT TECHNICAL COMMITTEE

Sidney Goldstein, D. Sc., Duramed Pharm.

Captopril	22 ANDA approvals
Sites	22 possible different manufacturing plants
Components/ Composition	22 possible different
Container/ Closure	How Many Different Materials/Sizes?
Bioequiv.	22 studies
NDS Sources	How Many Different Manufacturers?

ADDITIONAL EXAMPLES OF MULTIPLE GENERIC APPROVALS

<u>DRUG</u>	<u>NO. OF APPROVALS*</u>
Acylovir Caps.	Eight
Acylovir Tabs.	Five
Cimetidine Tabs.	Nine
Etodolac Tabs.	Ten
Ranitidine Tabs.	Twelve
Selegiline Tabs.	Seven
Diclofenac Delayed Release Tabs.	Seven

* Approvals after January, 1995

Dennis M. Erb, Ph.D.
Director
Regulatory Affairs

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West Point PA 19486
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March 23, 1999

Ms. Kimberly Topper
Center for Drug Evaluation and Research
HFD-021, Room 1091
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



**Re: Scientific Issues Related to
"Site-Specific Stability Data for
Drug and Biologic Applications"
Section of Draft Guidance and
Possible Revisions**

Merck & Co., Inc., is a worldwide research intensive company that is a leader in the U.S. pharmaceutical industry in discovery, development, production and marketing of human and animal health products. Since 1992, we have filed and received approval for thirteen original NDAs, and these products have been successfully launched; based on this experience, we feel qualified to comment on the FDA draft proposal related to the requirement for site stability data as an integral part of a CMC NDA package. We have worked with the Agency, both through correspondence and meetings in an effort to better define the "value add" of site specific stability during the NDA review process. We have been unsuccessful in defining with the Agency any scientific or technical benefit to be gained in product quality, or patient protection by this new requirement.

Development time for a pharmaceutical product, particularly for a new chemical entity is extremely long, generally 5-7 years. As part of the development, extensive work is done to fully characterize both the API and the drug product, together with stability profiles, and to understand the manufacturing processes, including process parameters and potential environmental sensitivities. The collection and evaluation of in-process test results, release results and stability information associated with all stages of product development are used to demonstrate the integrity of the process and the product. It is also used to determine specific sensitivities which must be controlled during further process scale-up and/or transfer to other manufacturing sites. The validity of this development scheme has been evidenced 13 times in the last 7 years at Merck with the successful transfer of processes and products to multiple manufacturing sites. In none of these cases were there any stability concerns.

The assumption by the FDA that site specific stability data provides an added assurance of product quality or successful transfer of technology is inaccurate. In most cases the

greatest challenges for successful validation are scale up issues, rather than site specific concerns. Site stability is not a scientifically appropriate measure of successful technology transfer. Stability is a function of the intrinsic molecular structure of the bulk substance, the composition of the formulation, the environment and storage conditions; all of these parameters are clearly defined as part of the development program and provide a significant body of knowledge about the product and its manufacturing process. None of these conditions are changed during technology transfer. Validation of a process using pre-defined processing parameters and quality attributes is the most relevant measure of successful technology transfer. Release of the validation lots meeting all critical quality attributes demonstrates that the product to be marketed is comparable to the biobatch and material used in the pivotal clinical studies.

The Agency has provided no scientific rationale as the basis for site specific stability beyond the “difference factor”- potential differences in the site technical staff, SOPs, raw materials etc. It is not logical to assume that technology transfer within a site is more or less rigorous than between sites. At Merck the site technical staff in most cases, reports into a central organization, common consistent SOPs exist between sites, common suppliers of raw materials are used and common specifications, test methods, audit procedures exist to assure control. In all cases representatives from Research & Development are actively involved in all process demonstrations and validation exercises for new product introductions into manufacturing, regardless of site location.

Merck recognizes the importance of stability data to support registration of a new drug product and fully supports the ICH recommendations. Prior to approval, we collect probe stability data during early development and generally at least 12 months stability data on three batches, at least two of which are manufactured at 1/10th production scale, using the final composition and process. This significant body of data permits a full understanding of the stability profile of the drug product. After approval, stability data are collected on the first 3 commercial scale batches manufactured at each site under accelerated and long-term storage conditions, and a commitment is made in the NDA to continually place on stability at least one batch every year. The Agency’s request for 3 month additional site specific stability does not add to our stability knowledge base, nor is this information the appropriate measure for success of technology transfer.

To remain competitive in the global market, Merck frequently uses multiple manufacturing sites for each of its products. However, our Research and Development and pilot plant facilities are limited in number and are not necessarily located at the final site of manufacture. The requirement for three months stability data on drug product made at the final facility with API from the final manufacturing site would have a major impact financially and on our timeline for regulatory filings. In many cases, in order to have API available for the site stability lots, construction of the API facility and the commitment of funds[\$5-10 million at risk] for construction would have to begin 6-10 months prior to the beginning of Phase III clinical studies. This timing is before we have the final dose selected, or have even demonstrated full safety and efficacy of the product. Without this acceleration of construction for both the API and the drug product facilities,

filing of the NDA could be delayed 6-9 months beyond completion of the clinical program. In most cases the lots made for the site stability studies would not be saleable, as they would be too close to expiry at the time of NDA approval. The significant economic investment that is required by these proposed regulations does not serve to add any level of assurance that technology transfer has been successful.

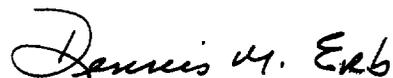
Merck strongly opposes the requirement of site specific stability as part of a NDA filing and approval. We believe such a requirement has no scientific justification, does not improve product quality or add to the safety or efficacy of the product to the patient. While we recognize the Agency's need to assure that material to be marketed is comparable to that which is used in the clinic, we would propose as an alternate:

At least three months prior to the FDA "PDUFA Due Date", the applicant will provide release data and a summary report of validation on at least three lots of API and three lots of drug product made at production scale in the final manufacturing equipment at the final manufacturing site. These validation lots will be placed on accelerated and long term stability as a NDA commitment.

In summary, Merck believes that 3 (or 6) months site specific stability data do not provide assurance of product quality or demonstrate successful transfer of technology. These attributes can be demonstrated only through successful validation of the processes at full scale in the final manufacturing equipment at the final facility. We believe that in virtually all instances of purported site-stability failures, the failures actually reflect situations that could and should have been flagged during process validation. We would propose as an alternative that release data and a summary of the validation study be available for review by the Agency three months prior to the PDUFA Due Date.

We appreciate the opportunity to participate in the March 31, 1999 public meeting to further discuss the scientific issues related to "Site-Specific Stability for Drug and Biologic Applications".

Sincerely,



Dennis M. Erb, Ph.D.

Senior Director
Regulatory Affairs

Site Specific
Stability Data for Drug and
Biologic Applications;
Public Meeting

Dr. Tony Amann

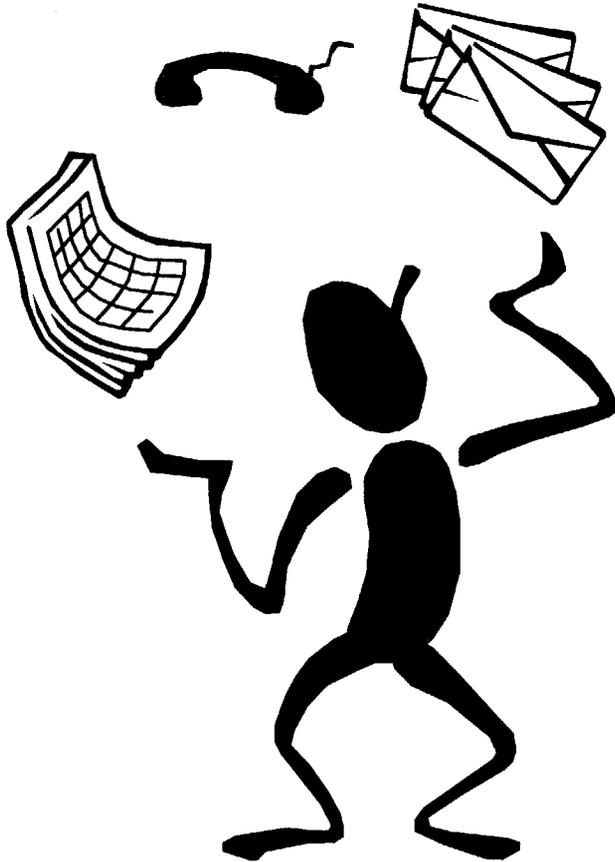
NAPM

March 31, 1999

Site Specific Stability Data-Topics

- General Considerations
- Review Original Rationale-Issues
- Changes Implemented Since Original Rule
- FDA-MA Impact
- GMP (District) Vs. Submission (CDER)
- Recommendation

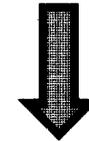
Recap--Rationale for SSS



Old Practice

Small Dosage Units

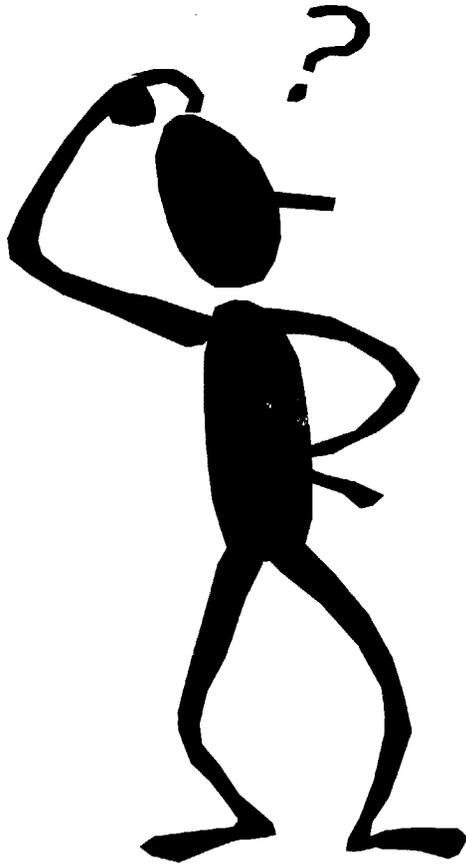
Site A



Production Dosage Units

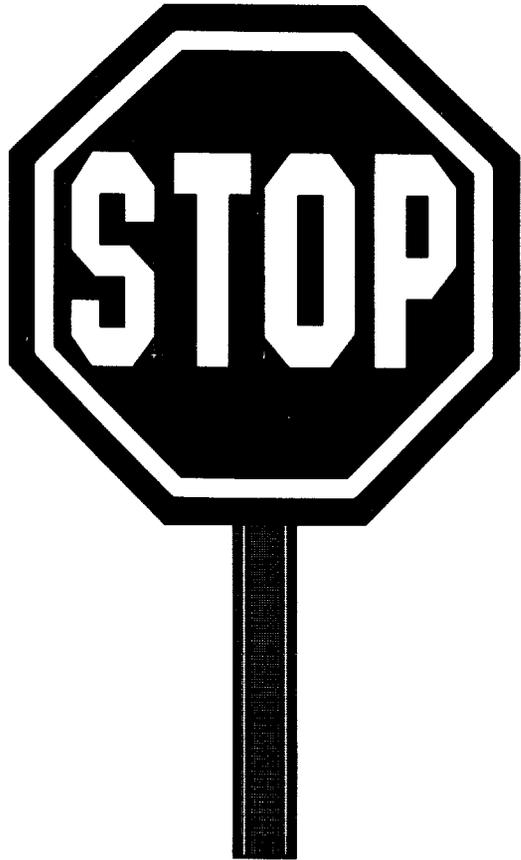
Site B

Early Issues--FDA



- NO 100,000 or 10% batch limit
- NO Process Validation
- Changes in Site
- Changes in Manufacturing Procedure
- Changes in Formulation
- Bulk Hold
- NO Statistical Sampling
- NO Pre-Approval Inspection
- CDER Vs. District Responsibility Unclear

Results.....



Manufacture Submission
Batches at the Site you
will Manufacture
Marketed Product Using
Similar Equipment



Site Specific Stability

Site Specific Stability

We Have Come a Long
Way

Changes That Have Occurred

- Minimum Unit Size or 10% Batch Size
- Process Validation
 - Submission batch
 - First three production batches
- Pre-Approval Inspections
- SUPAC, BACPAC

Changes That Have Occurred--CTD

- Guidances
 - ICH
 - Packaging
 - Stability
- FDA-MA

Review of Issues

Issues

Addressed by

A. Small batch Size	A. Minim. Batch size or 10%
B. No Process Val	B. Process Val-first 3 batches
C. Changes In Site	C. SUPAC
D. Changes in Manuf. Procedure	D. SUPAC
E. Changes in Formulation	E. SUPAC

Review of Issues-- CDER.

Issues

- F. Bulk Hold
- G. Statistical Sampling
- H. Review of
information prior to
marketing
- I. CDER Vs. District
Responsibilities

Addressed by

- F. Packaging Guidelines
- G. Packaging Guidelines
- H. Pre-Approval
Inspections
- I. Issue??

Site Specific Stability Recommendation

Recommend for FDA to Reevaluate their
Position on Site Specific Stability in light of
All the Guidances and Regulations in Place.

Site Specific Stability should not
be a Requirement for Initial
Regulatory Submission Batches

Merck Presentation to the FDA Meeting on Site Stability

03/26/1999

Dr. Tway

OPH #5
Dr. Tway

FDA Proposal:

3 months accelerated data

Drug product

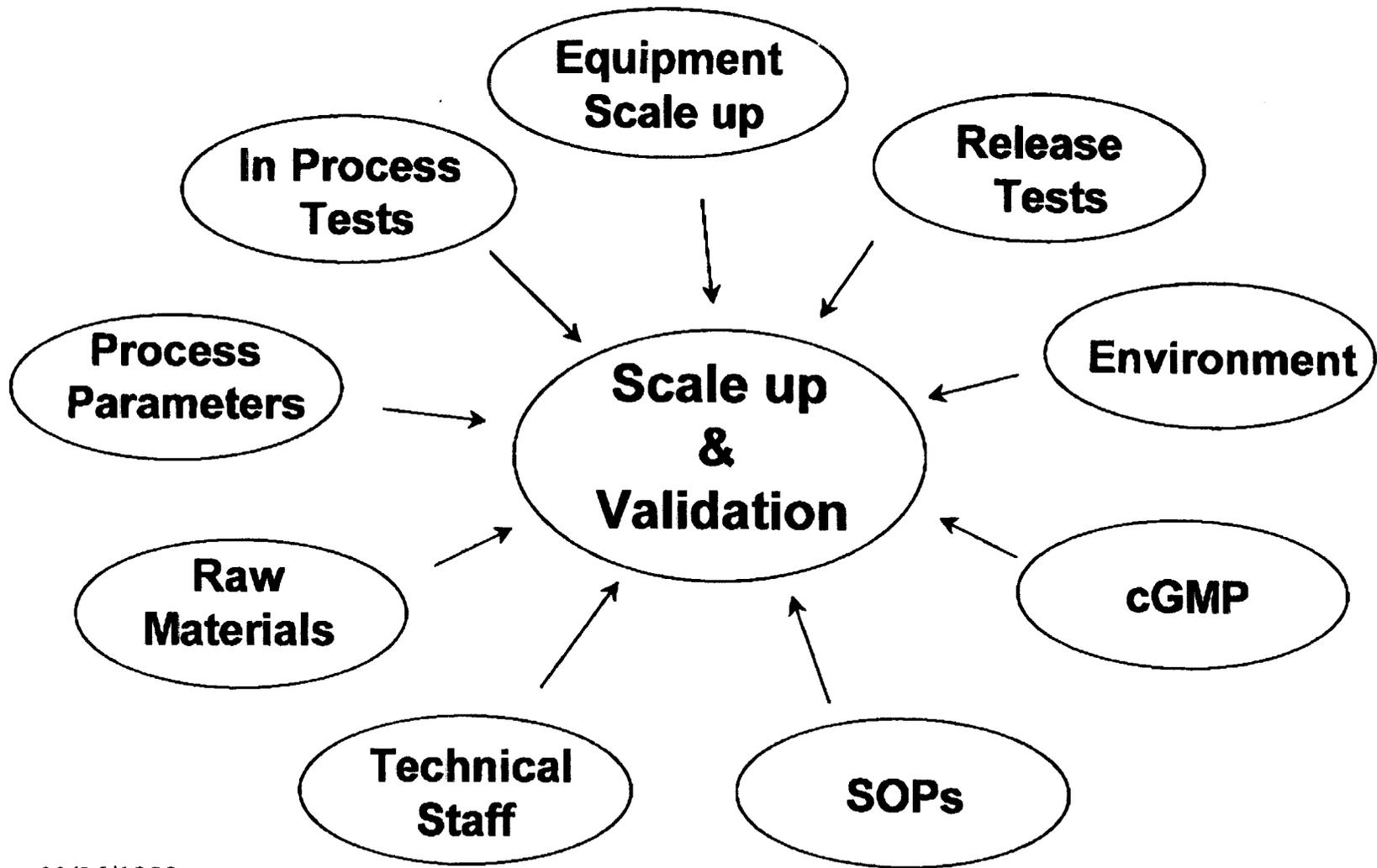
Manufacturing site

**Drug substance from
manufacturing site**

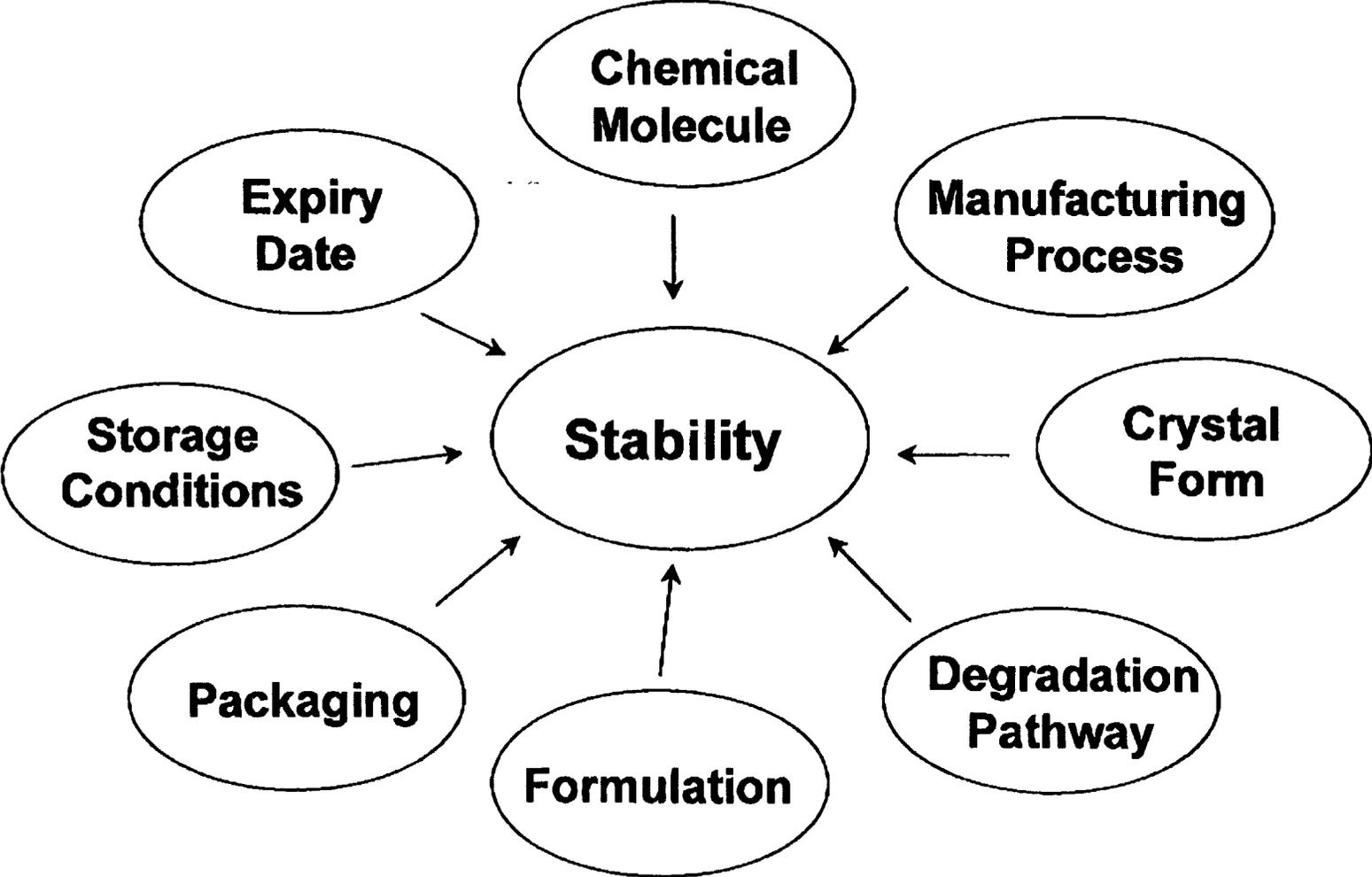
Not necessarily at full scale

Not necessarily in commercial equipment

Validation Measures Success of Process Transfer



Stability Defined during Development



Stability Results

	<u>MCSS</u>			<u>Production Batches</u>		
	Months	Assay %	Degradates %	Months	Assay %	Degradates %
CRIXIVAN	0	99.3	0	0	101.9	0
	24	100.0	0.7	24	98.3	0.4
COZAAR	0	98.9	<LOQ	0	99.6	<LOQ
	24	98.6	<LOQ	24	99.5	<LOQ
AGGRASTAT	0	99.0	<LOQ	0	98.8	<LOQ
	12	101.1	<LOQ	12	99.4	<LOQ
TIM. XE	0	100.6	<LOQ	0	98.0	<LOQ
	24	101.1	1.4	24	100.2	0.8
MAXALT	0	101.1	<LOQ	0	100.1	<LOQ
	18	100.5	<LOQ	18	100.5	<LOQ
SINGULAIR	0	101.7	0.1	0	99.9	0.3
	12	98.9	0.5	12	99.0	0.4

03/26/1999

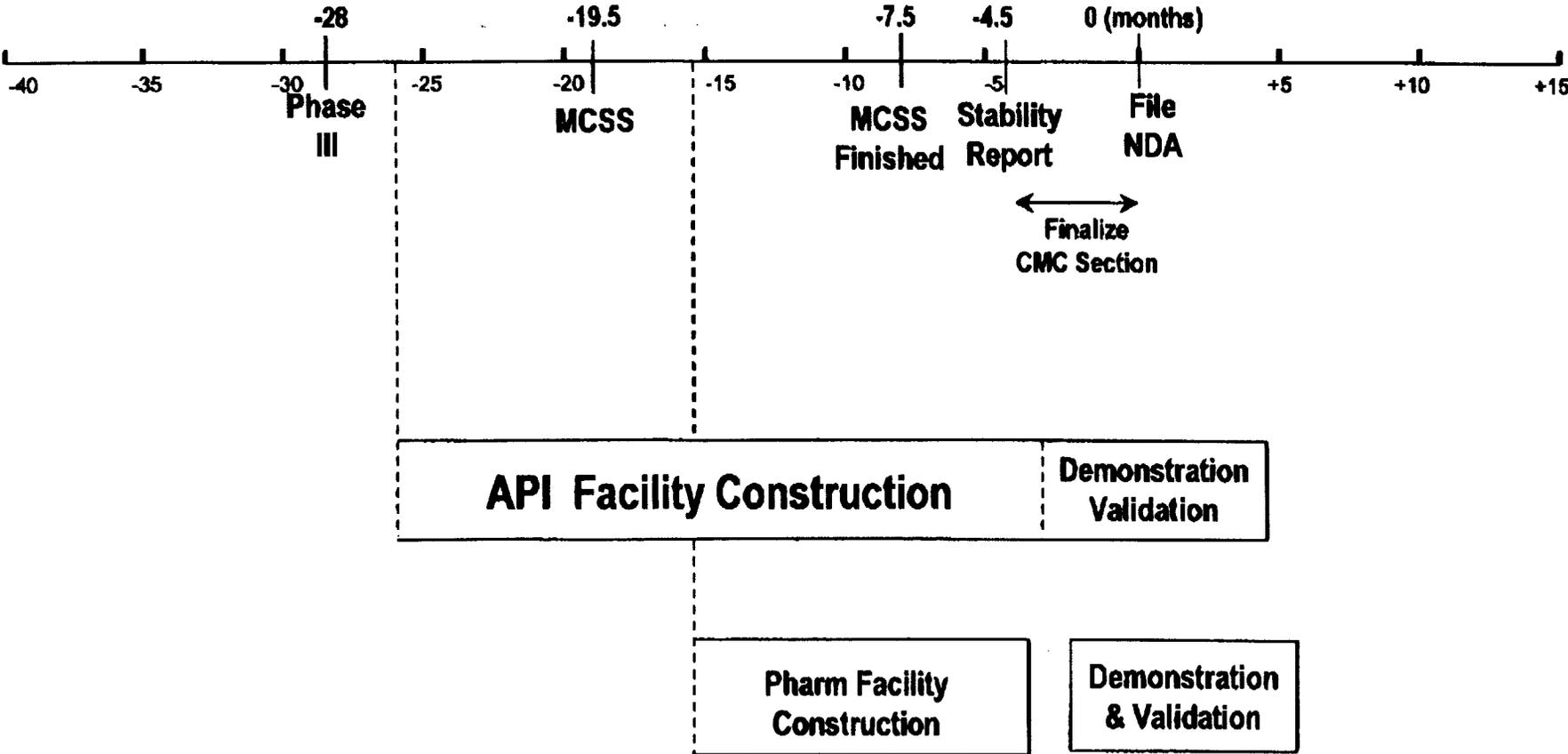
This proposal has major impact:

- **Facilities available**

Financial

Time to File

Development Time Line

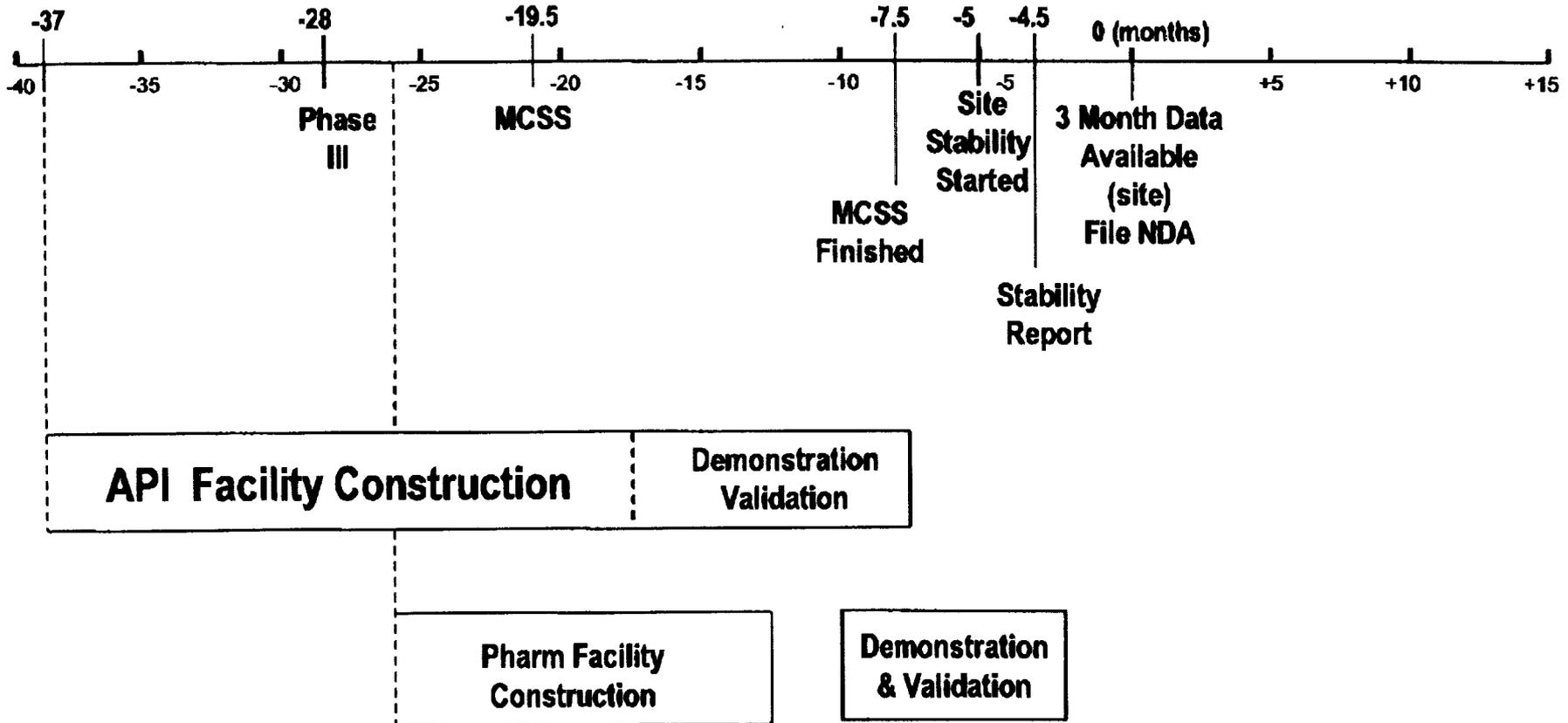


+4
|
**Site
Stability
Started**

+9
|
**3 Month Data
Available
(site)**

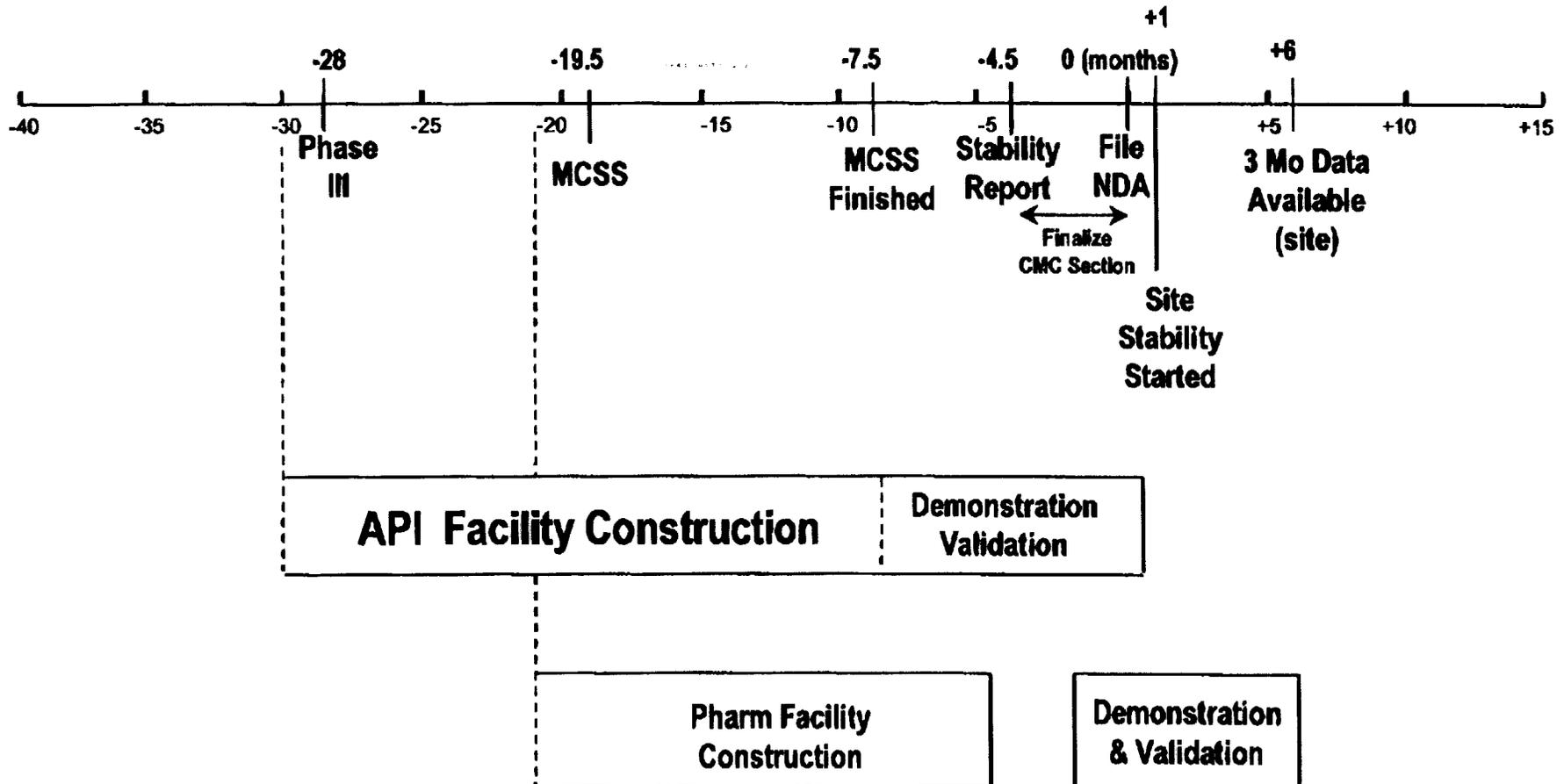
03/26/1999

Development Time Line



03/26/1999

Development Time Line



03/26/1999

Alternate proposal:

- **3 months prior to PDUFA date**
- **Release data and validation report summary**
 - 3 API lots**
 - 3 Drug product lots**
- **Production scale**
- **Final manufacturing equipment**
- **Final manufacturing site**

Presentation to the FDA Public Meeting on Site-Specific Stability

Pharmacia & Upjohn Inc.

OPH #7
Pharmacia & Upjohn

A Site-Specific stability requirement

is an answer in search of a
question

What would site-specific stability add to the existing stability performance profile of a product?

- Stress stability studies
- Stability of clinical batches
- Degradation products identified and qualified
- Supportive stability studies
- Primary stability studies

The Stability Performance Profile is used to determine:

- Specifications
- Packaging and storage conditions
- Initial expiration dating period

3 months of site-specific stability would not add any meaningful knowledge

What would site-specific stability add to the Process Performance Profile of a product?

The Process Performance Profile of a product is a compilation of knowledge gained from a continuum of process development and validation.

Laboratory → Pilot Plant → Manufacturing

Identifies:

- Equipment and conditions for robust process
- Critical quality attributes
- Critical process parameters

This part of the Process Performance Profile forms the basis for scale-up and technology transfer plans and the process validation protocol.

3 months site stability does not add knowledge

What would site-specific stability add to the quality of the product from the manufacturing site?

- Environmental and in-process controls, specifications are derived from the SPP and PPP
- Validation protocol demonstrates reproducibility of process and equivalence of the product on scale-up
- Success of scale-up and technology transfer judged by consistency of quality attributes for full scale and validation batches - not by site specific stability

Stability at the final manufacturing site

- Firm obligated to place the first 3 full scale batches on stability
- Shared risk - It is contrary to our firm's best interests to risk launching a new product only to have to recall it due to inconsistent stability performance

Summary

Development of the SPP and PPP for a product is a cumulative process during drug development which results in:

- thorough understanding of product stability
- thorough understanding of the process

Success of technology transfer/scale-up relies on that knowledge and demonstration of process robustness through Process Validation in the final manufacturing plant

**A site specific stability requirement is an
answer in search of a question**

.....and there is no question

**Draft Guidance for Industry on Stability Testing of
Drug Substances and Drug Products -
Site Specific Stability Data**

Taylor Burtis
Manager, Regulatory Affairs -Policy
Genentech, Inc.



GENERAL COMMENTS

- Current Draft Guidance maybe more appropriate for stability program of small molecule pharmaceuticals or where characterization or lot release data are not adequate to support equivalence.
- Recommend separate guideline for proteins, polypeptides, their derivatives, or any "well-characterized" pharmaceutical produced using rDNA technology



Section on: Site Specific Stability Data

- For a well characterized molecule with a defined stability profile:
 - Genentech does not agree with the Agencies exemption of Biologics from providing accelerated data.
 - Accelerated data provides worse case scenario
 - Valuable in accessing process related changes
 - It has been Genentech's experience that for proteins accelerated degradation profile provides adequate SSS data within one month.



Section on: Site Specific Stability Data

For SSS accelerated data:

- Recommend that the time interval for conducting accelerated studies be based on the characterization and profile of the molecule not on an arbitrary time interval.
- Recommend that accelerated data on one site-specific batch, in addition to sufficient characterization data to demonstrate equivalence, be part of the submission.



For Well Characterized Molecule

- The guidance recommends that as part of the submission for a new site 12 months of site-specific stability data on three primary batches be submitted.
 - Genentech has seen no evidence of site changes effecting stability.
 - We recommend that four to six months of real time SSS data, at time of approval, on one lot of site specific product be submitted with the commitment to notify FDA if the profile changes. Any additional lots put on stability would be excessive and provide no scientific added-value information.



In Summary

- Recommend for a well characterized molecule manufacturing site change that approval be based on:
 - one month of accelerated data on one batch lot be provided in the submission and,
 - 4-6 months of real time SSS data on one batch be provided during the review period.



Site-Specific Stability

Analytical Issues

Robin Roman

Method Transfer

- Prospective protocol for transfer of methods
 - extensive cross-validation testing
- Assurance that a new site can perform the methods is Good Business Practice

Specifications

- Developed over years of prior experience
- Part of guarantee of safety and efficacy
- Approved by FDA to ensure *sameness* of drug substance and drug product

Stability Testing of First Commercial Batches

- Methods and specifications approved by FDA
- ICH stability conditions are “worst case”
 - product in commerce maintained at less severe conditions
- Shelf life established during development and ensured by process validation

Good Science, Good Regulation

- “One of FDA’s traditional strengths has been the quality of the science underlying its decisions.”
- “A strong scientific infrastructure... supports the development of science-based guidance”
- The Agency has not provided a scientific rationale as the basis for site-specific stability requirements

Proposal

- Establish the scientific basis for requirement of site-specific stability
- Use the ICH Q1A EWG to resolve the site-specific stability issue