M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: March 6, 2001

To: Dockets Management Branch (HFA-305)

From: Melissa Lamb
Office of Generic Drugs

Subject: History of Supac

This memorandum forwards overheads of a presentation to the Dockets Management Branch for inclusion in Docket 90S-0308. The following is information on the presentation for the Docket records:

Title of Presentation: History of Supac

Presented for: Industry Exchange Meeting

Date Presented: April 20, 2000

Presented by: Vilayat S. Sayeed, Ph.D.

Number of Pages: 48

Melissa Lamb

Attachment

90S-0308

M700

FDA/ISPE Scale-Up Post Approval Changes
Industry Exchange Meetings
Chicago, Illinois
April 20, 2000

HISTORY OF SUPAC

Vilayat S. Sayeed, Ph.D.
Office of Pharmaceutical Science
Center for Drug Evaluation & Research
Food and Drug Administration

Purpose of SUPAC

- Maintain Safety, Efficacy, Quality
- Provide Regulatory Relief/Flexibility

Purpose of SUPAC

- The Guidance Defines:

- Levels of change
- Recommended CMC tests for each level
- *in vitro* dissolution tests and/or *in vivo* bioequivalence tests for each level
- documentation that should support the change

SUPAC Covers

- components or composition
- site of manufacture
- scale of manufacture
- manufacturing (process and equipment)

Legal Effect of Guidance Documents

- They are not binding on the public or the agency
- They represent the agency's current thinking on the subject addressed in the document
- FDA will take steps to ensure staff does not deviate without appropriate justification and supervisory concurrence
- Alternate methods are acceptable

SUPAC - SCALE UP AND POST APPROVAL CHANGES

IMMEDIATE RELEASE	-IR	FINAL
SEMISOLIDS	-SS	FINAL
MODIFIED RELEASE	-MR	FINAL
MANUFACTURING EQUIPMENT ADDENDUM	-IR / MR	FINAL
MANUFACTURING EQUIPMENT ADDENDUM	SS Addendum in-progress	

SUPAC - PROCESS

- Research
- Workshop
- Draft published for comment
- Guidance finalized
- Internal training
- Industry training

SUPAC - PROCESS

- Central contact point - Nancy Sager, OPS
  - Questions
  - Proposals
- Database - History and tracking
- Evaluation/Decisions - OPS Chemistry Division Directors

SUPAC-IR - IMPLEMENTATION

- Federal Register notice - November 30, 1995
- Industry training - February 15, 1996
- Updated via letter - February 18, 1997
- WG revising the guidance
- Applies to immediate release tablets, chewable tablets, capsules, and soft gelatin

SUPAC-SS - IMPLEMENTATION

- Federal register notice - June 13, 1997
- Industry training - May 29, 1997
- Applies to non-sterile semi-solid preparations, e.g., creams, gels, and ointments

SUPAC-MR

- Federal register notice - October 6, 1997
- Industry training - November 24, 1997
- Applies to modified release, solid, oral dosage forms

SUPAC - FDA PERSPECTIVE

- Benefits/Successes
  - Uniform approach
    - Defines - Data/Documentation Submission Type
  - Provides relief to the industry
    - Timeliness
    - Planning
    - Costs/Savings

Survey of 6 Pharmaceutical Companies

- Conducted by FDA's Office of Planning and Evaluation with assistance from the Eastern Research Group, Inc.
- Company representatives praised FDA for establishing a uniform policy for post approval CMC changes and for bringing openness, consistency, and clarity to the regulatory requirements.
- SUPAC-IR's greatest impact lies in enhancing industry's ability to plan and implement change and manage its resources efficiently.

SUPAC - INDUSTRY PERSPECTIVE

- Interviews with 6 companies, first half 97
- Shorter waiting times for site transfers
  - Reducing operating, overhead, and maintenance expenses
- More rapid implementation of process and equipment changes
  - Improved yield
  - Reduce failure investigations
- More rapid implementation of batch size increases

SUPAC - INDUSTRY PERSPECTIVE

- Production of fewer unmarketable stability batches
  - Reduce stability testing/costs
- Reduced administrative costs for documentation of changes by the regulatory affairs departments
- Estimated saving $51.2 million/year

SUPAC - FDA PERSPECTIVE

- Problems/Failures
  - New approach - confusion
  - Resources
    - Development
    - Implementation
    - Maintenance
  - Expectations
  - Utilization

First SUPAC Workshop: December 1991

- Co-sponsored by AAPS, FDA, and USP
- Primary focus:
  - Oral solid dosage forms
  - Type of additional information needed to document identity, strength, quality, purity, and potency
- Workshop Report published in 1993
- SUPAC-IR Guidance final November 1995
- Letter to Industry February 1997

SUPAC Initiatives
What is SUPAC Guidance?

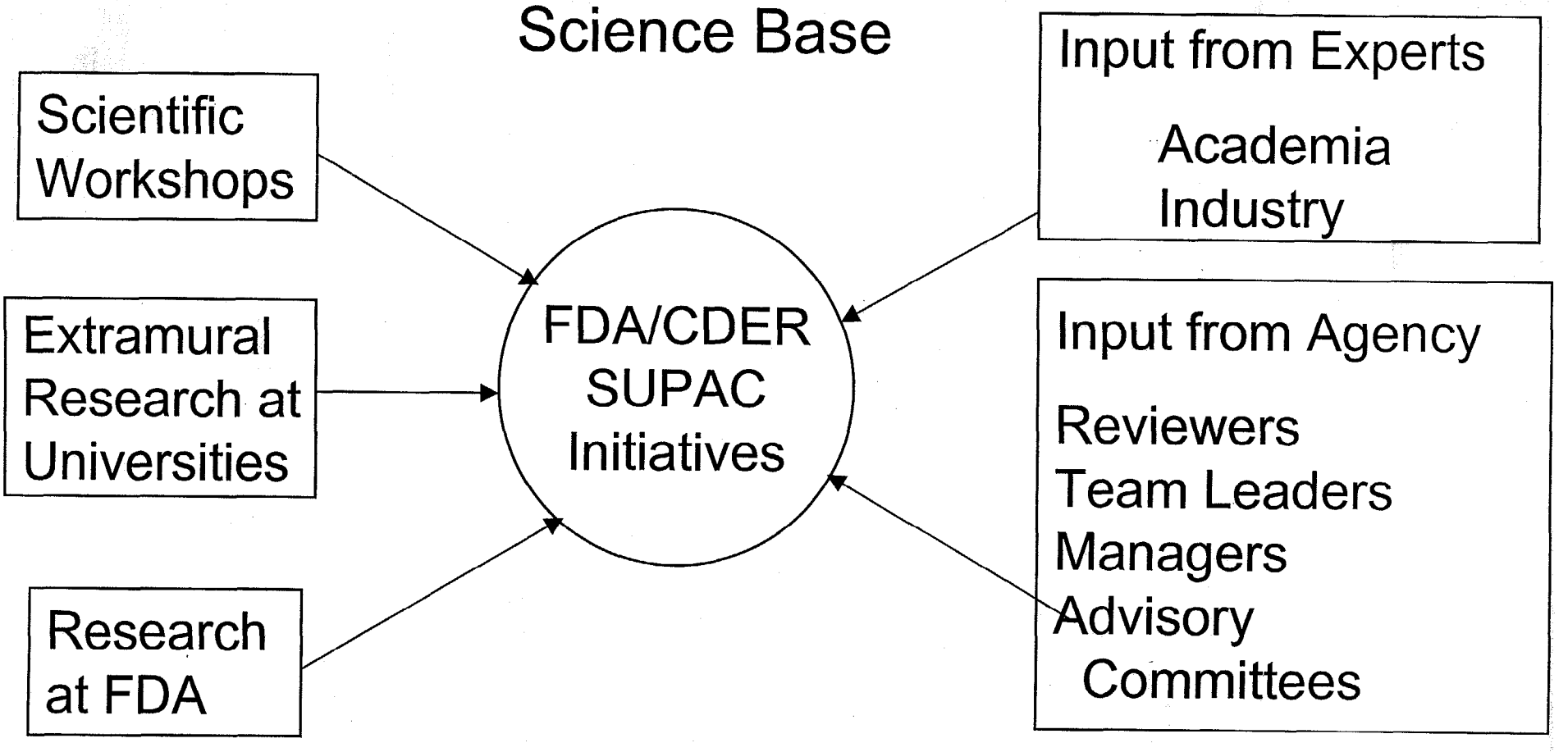
- Communication that represents the best scientific judgement of the Agency at this time
  - informal
  - non-binding
  - aimed at lowering regulatory burden

SUPAC - INITIATIVES

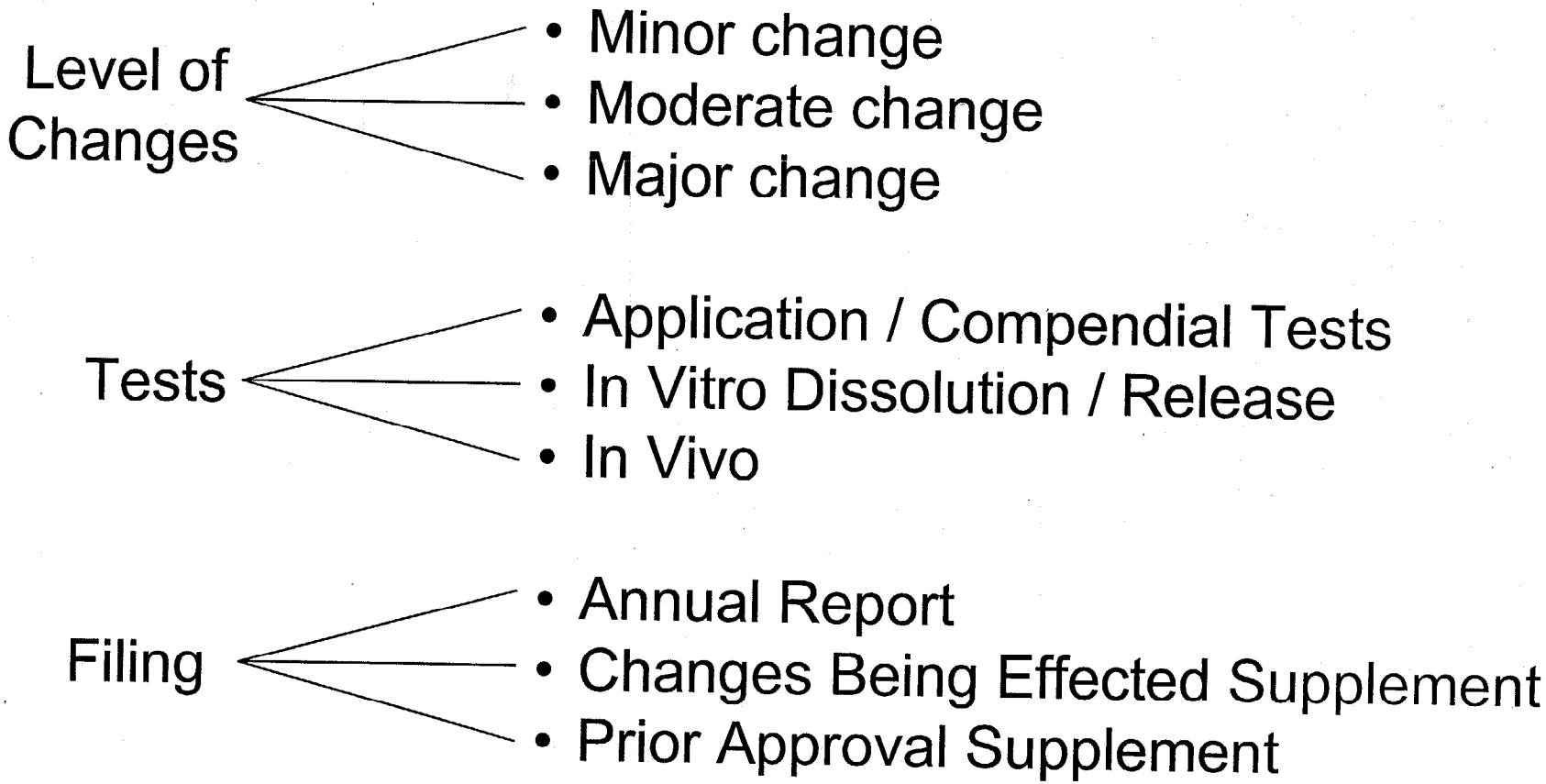
Model for Developing Guidance

- Recommendations of a Scientific Workshop as a base
- Site visits and Discussions with Industries
- Research at FDA and Universities
- Interactive discussions and significant input from Academia & Industry during Guidance development
- Input from Advisory Committees

SUPAC - INITIATIVES



SUPAC - INITIATIVES



SUPAC - INITIATIVES

Quality and Performance

Impact

Significant

Not Detectable

Level 3
likely to have significant impact

Level 2
could have significant impact

Level 1
unlikely to have notable impact

Probability

Likely

Not Detectable

SUPAC -IR

- Biopharmaceutics Classification System
  - Solubility
  - Permeability
  - Dissolution
- Dissolution Profile Comparison
  - Similarity Factor, f_2

SUPAC - INITIATIVES

- SUPAC guidances provide 'how to' recommendations on documentation of product sameness and equivalence in the presence of post-approval change(s).
- Product sameness based on in vitro dissolution profile comparison in multi-media.
- Product sameness based on equivalence approach of comparison of in vitro release rate.

SUPAC - INITIATIVES

Dosage Form	AAPS / FDA Workshop	Workshop Report In Pharm Research:	SUPAC Guidance Date Issued
Immediate Release	Dec 11-13, 1991	10:313, 1993	SUPAC-IR November 1995
Extended Release	Sept 8-10 1992	10:1800, 1993	SUPAC-MR, September 1997
Liquid & Semisold Disperse Systems	May 24-26 1993	11:1216, 1994	SUPAC-SS May 1997

PRODUCT SAMENESS

An attribute of products indicating that they will perform in a similar manner in terms of physicochemical properties and is presumed to allow a link back to the batches tested for safety, efficacy or bioequivalence.

Product Sameness =	Requalifying (approved) Product after 'change'
Immediate Release Products:	In Vitro Dissolution Tests
Modified Release Products:	In Vitro Dissolution Tests
Semi-solid Dosage Forms:	In Vitro Release Test

Presentation to the Advisory Committee for Pharmaceutical Science

- June 24, 1998
- SUPAC-IR Revision Objectives
  - Improve its utility
    - Re-evaluate Case C dissolution
    - Optimize change levels based on available research data
    - Introduce "multiple changes"
  - Consolidate "lessons learned" during implementation
    - Address industry questions and comments

Presentation to the Advisory Committee for Pharmaceutical Science Case C Dissolution

- Dissolution profiles in five media
  - Water
  - 0.1 N HCl
  - pH 4.5
  - pH 6.5
  - pH 7.5
- f2 ' 50
- Level 2 Components & Composition changes for products of *low solubility-high permeability* drugs
- Level 2 Equipment changes for products of all drugs

Presentation to the Advisory Committee for Pharmaceutical Science

- Options for Modifying Case C Dissolution
  - Two media
    - Weak acids: application/compendial media plus a more acidic pH (1 or 3)
    - Weak bases: application/compendial media plus a more alkaline pH (6.8 or 7.5)
  - Three media
    - pH 1, 4.5, and 7.5
  - When the application/compendial media contains a surfactant?

Presentation to the Advisory Committee for Pharmaceutical Science

- Change Definitions
  - Re-evaluation of change definitions
    - FDA-UMAB research data plus further explorations of in-house data
    - Accommodate multiple changes
      - Multiple change level to be the highest level of an individual change in a series of changes
    - Components & composition
    - Batch size
    - Equipment
    - Process
    - Site

Presentation to the Advisory Committee for Pharmaceutical Science Batch Size Changes

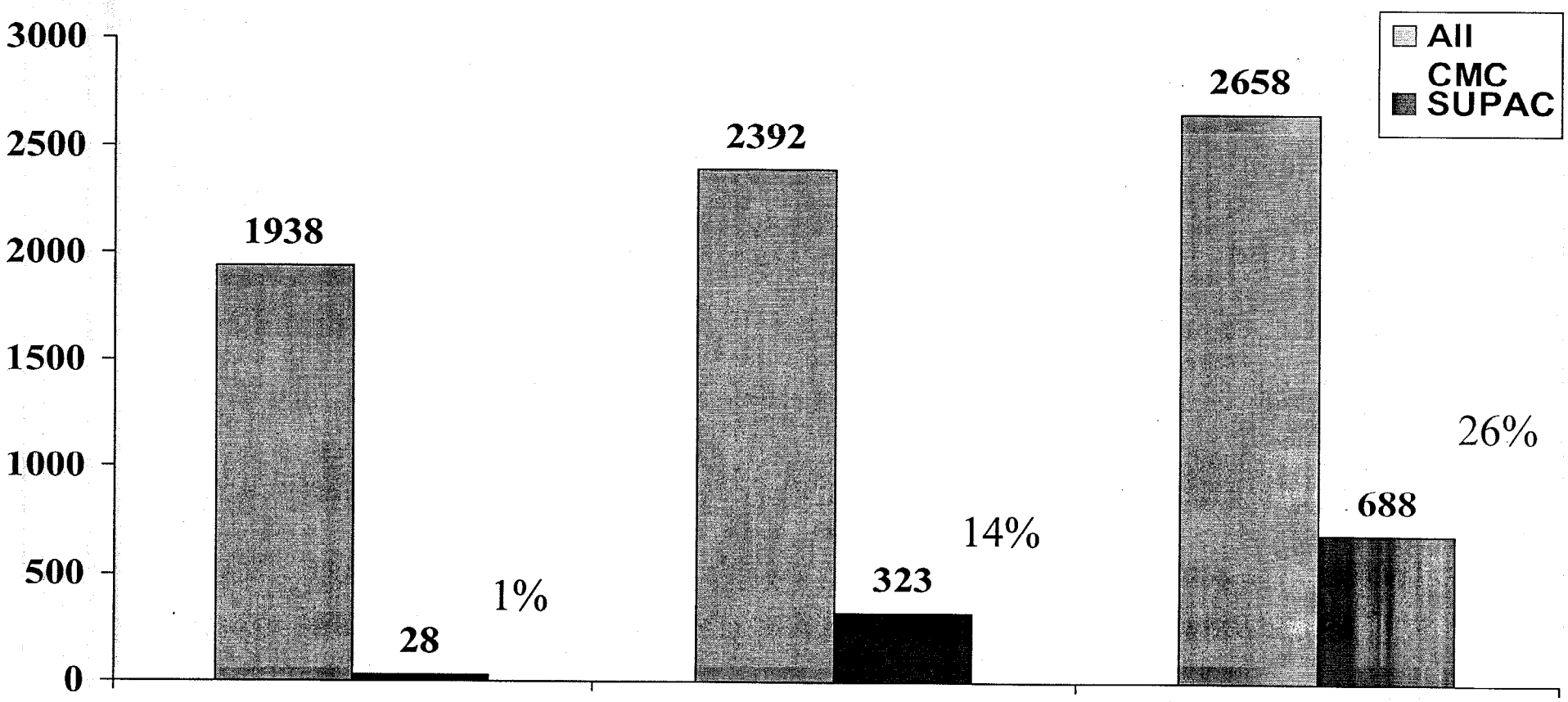
- Biobatch ' 100K units
- Scale-up factor: 10X
- Research data suggests 10X is conservative
- Small batch size for research formulations
- Changes in batch size are associated with changes in equipment and process parameters

- Is it appropriate to define batch size as a multiple equipment and process change?
  - Proposed level 1: Batch size change accomplished using equipment of similar design and same operating principle, and changes in processing parameters to meet in-process and final product specification

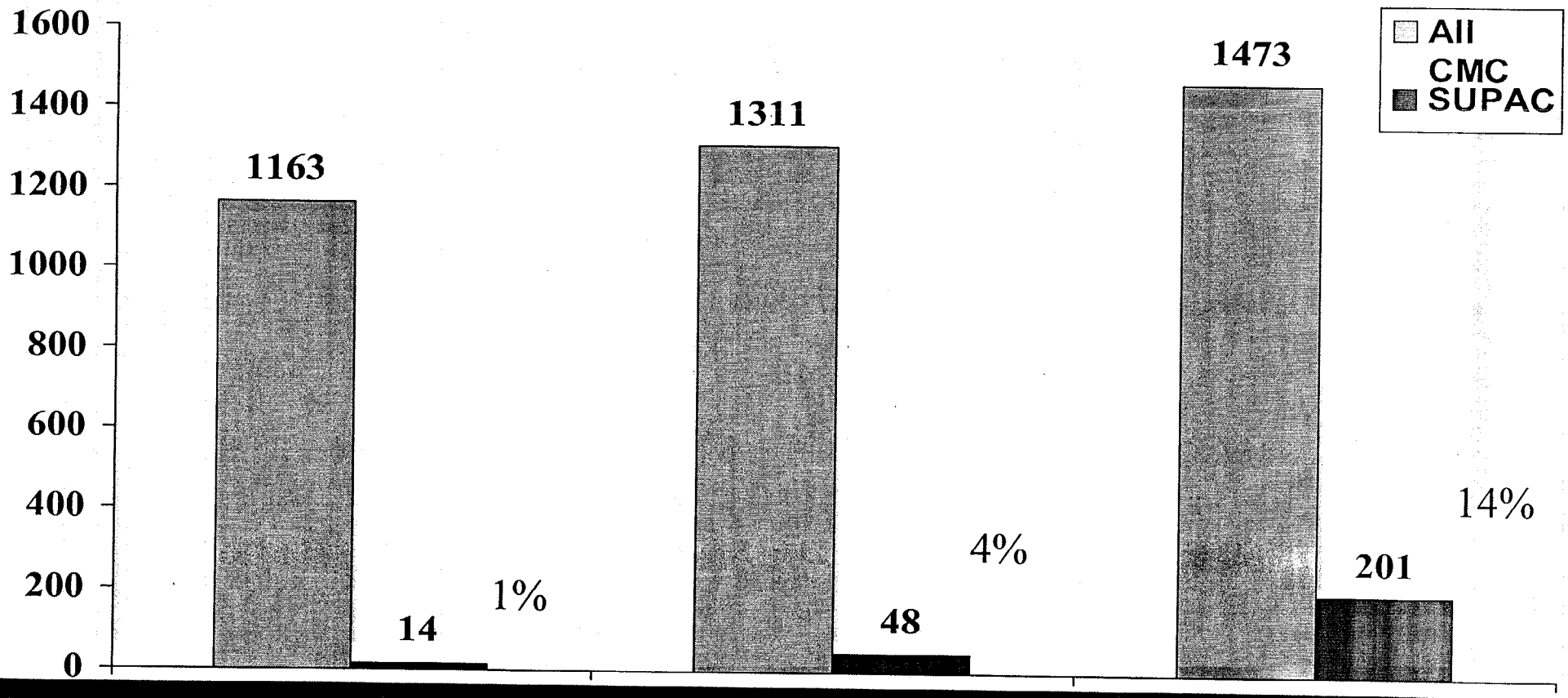
OUTCOME OF ADVISORY COMMITTEE

- Draft SUPAC-IR revision
  - Case C Dissolution
    - For products containing low solubility and high permeability drug substances
    - Application or compendial test method plus pH 1.0, 4.5, and 6.8
  - Batch size (scale up/scale down)
    - Addressed as multiple changes in equipment and process

Percentage of ANDA Chemistry Supplements Submitted as SUPAC



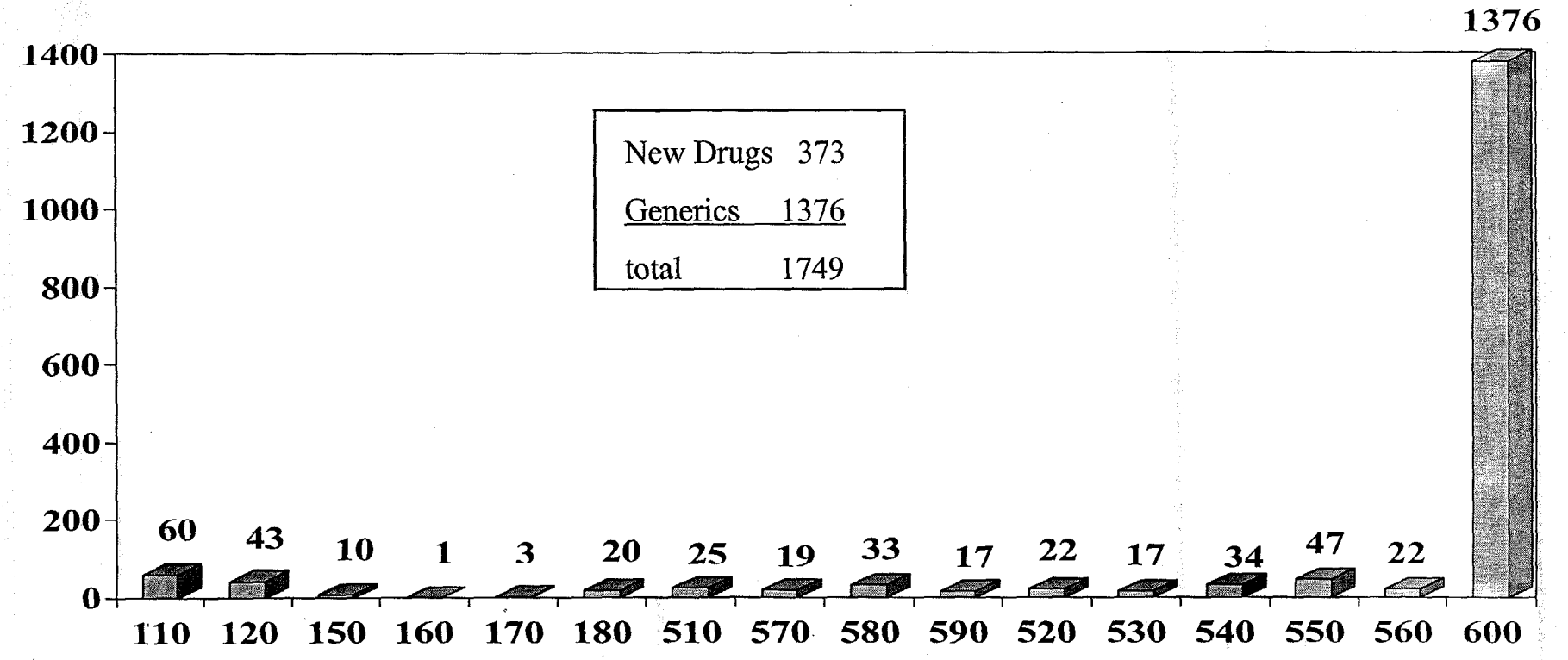
Percentage of NDA Chemistry Supplements Submitted as SUPAC



SUPAC SUPPLEMENTS RECEIVED

BY DIVISION

(1 Dec 95 - 31 Jul 99)



Division Number Corresponding Therapeutic Area

110 - Cardio-Renal

120 - Neuropharmacological

150 - Oncologic

160 - Radiopharmaceutic, Medical Imaging

170 - Anesthetic, Critical Care, Addiction

180 - GI and Coagulation

510 - Metabolic and Endocrine

520 - Anti-Infective

530 - Anti-Viral

540 - Dermatologic and Dental

550 - Anti-Inflammatory, Analgesic, Opthalmologic

560 - Over-The-Counter

570 - Pulmonary

580 - Reproductive and Urologic

590 - Special Pathogen and Immunologic

600 - Generics

•All SUPAC submissions should contain the following information:

- For supplements, a brief description of changes addressed in the submission should be included in the cover letter. For annual reports, it should be in the summary description of the changes described in the report.
- A reference identifying the specific section of the SUPAC guidance used as the basis for the submission.

Common Reasons For CBE Non-qualifications And Misfilings

- 1996
  - Multiple change includes level 2 equipment change (PAS)
  - Insufficient chemistry documentation (e.g., missing production batch records or dissolution)
  - Deletion of test
  - Stand alone packaging operation site change
  - Insufficient information for proposed site

Common Reasons For CBE Non-qualifications And Misfilings

- 1997
  - Multiple change includes level 2 equipment change (PAS)
  - Stand alone analytical site change
  - Deficient chemistry documentation (e.g., stability, dissolution, blend uniformity and certificate of analysis)
  - Binder change (PAS)
  - Wrong dosage form (e.g., oral suspension product)

Common Reasons For CBE Non-qualifications And Misfilings

- 1998
  - No current satisfactory GMP inspection for new site
  - Deficient chemistry documentation (e.g., stability, production batch records, dissolution, or comparative data for biological tests for a new test facility)
  - Multiple change includes Container / closure change
  - Wetting agent change - not covered by SUPAC

SUPAC Supplement Decisions

- Cumulative Decision Results as of 31 July 99:
  - Approved / Approvable 95.0%
  - Withdrawn 4.5%
  - Not Approvable * 0.5%

    * 7 supplements not approvable:

      5 submitted as prior approval

      1 submitted as CBE that was denied

      1 submitted as CBE that was granted

HAS SUPAC AFFECTED CDER POLICY?

- Use of comparability protocols
- Extension of SUPAC philosophy to the 314.70 rewrite and guidance
- Extension of SUPAC philosophy to other types of changes and other dosage forms

FDA MODERNIZATION ACT OF 1997

- Section 116. Manufacturing Changes for Drugs
- A/NDA holder must validate the effects of change
- 3 Types of changes
  - Major
    - Prior approval supplements
  - Other
    - Changes being effected supplements (0 or 30-Day)
    - Annual reports

MAJOR MANUFACTURING CHANGES

- Prior approval supplements
- Substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug

MAJOR MANUFACTURING CHANGES

- Change in the qualitative or quantitative formulation or in the specifications
  - Unless exempted by the Secretary by regulation or by guidance
- Change determined by the Secretary to require completion of an appropriate clinical study demonstrating equivalence to drug before the change
- Changes determined by the Secretary by regulation or guidance to have a substantial potential to adversely affect the safety or effectiveness of the drug

OTHER MANUFACTURING CHANGES

- Changes not requiring supplemental applications
  - Annual report
  - Include the same information as for a supplement
  - May report more than one change in an annual report

OTHER MANUFACTURING CHANGES

- Changes requiring a supplement
  - Contains same information as prior approval
  - Distribution may begin 30 days after receipt
  - Secretary may designate certain changes that can be made at time of submission
  - If disapproved, Secretary may order the cessation of distribution of drugs made with the manufacturing change

OTHER MANUFACTURING CHANGES

- A moderate change has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product - Changes being effected supplement
- A minor change has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product - Annual Report