International Journal

Generic2000Drugs

Drug Development & Manufacture for Pharmaceutical Research Scientists

Volume 03 2000
Number 08

International Journal

generic drugs

International Journal of Generic Drugs

Development and Manufacture of Generics and NDA CMC sections for the Pharmaceutical Scientist.

Features reviews and articles on Drug Development for the Pharmaceutical R&D, RA, QA and Manufacturing Scientist.

- Generic & Innovative Drug Development. - Formulations
- **Bioequivalency - IVIVC - CDPs**
- Quality Control /Assurance
- PAI Know How
- Microbiology Control
- Pharmaceutical Stability
- Regulatory Affairs
- Global Product Registration
- Bulk Pharmaceutical Chemical GMP/validation
- Features the *Ins-and-Outs* of **NDA CMC** Sections
- Generic Drug Manufacturing
- New Assays & Impurity Profiles

LOCUM Publishing House

ISSN 0793 694X US/Canada ISSN 0793-7784 Euro ISSN 0793-7822 Pacific Rim.

2000 International Journal of Generic Drugs

Electronic Journal on Disk

Journal on the Web

e- Journal

ISSN 0793 694X ; 0793 7784 ; 0793 7822

TABLE OF CONTENTS
2000- 2001 Issues

(Representative list of the current 2000 Table of Contents in Summary Form)

ISSN 0793 694X US/Canada ISSN 0793-7784 Euro ISSN 0793-7822 Pacific Rim

International Journal of Generic Drugs

OFFICIAL PUBLICATION OF THE INTERNATIONAL ASSOCIATION OF DRUG MANUFACTURERS

EDITORIAL

EDITOR-IN-CHIEF
JEREMY D BLOCK

The International Journal of Generic Drugs publishes articles reviews and papers on all aspects of Generic and Innovative Drug Development from pre-formulation to aspects of regulatory strategy. Emphasis is placed on the US and EU exposure of the Generic Drug Industry with special reference to the **on-time** development of **ANDA / EU** submissions. The Chemistry, Manufacture and Controls **(CMC)** section of **NDA** development cover *hands-on* nuts-and-bolts developmental issues that vary across the full drug development spectrum from documentation requirements, excipients specifications, development (pre-to-final) formulation, scale-up, analytical, cleaning and process **validation protocols** necessary for the **entire** drug development process. The overall objective in generic / CMC drug development is to get the newly developed product to the market place on time. The Journal attempts to clarify and simplify development and regulatory issues to achieve this crucial objective, as a major and vital **IT** provider .

Articles include pre-formulation; drug development; granule sampling; bioequivalence data; specific container closure aspects, and manufacturing techniques; Quality Control; Quality Assurance; comprehensive development analytical assay and impurity methodology via IAGIM, pharmaceutical stability in conjunction with regulatory requirements and model Abbreviated New Drug Applications. Three differing geographic editions (US & Canada; Euro; Pacific Rim) are published highlighting various technological interests specific to each area.

The Journal publishes Drugs-Off-Patent™ Special Reports up to the year 2016 including Currents Drugs in Today's Pipeline and holds updated lists and evaluation reports of Waxman/Gatt Patent/ Exclusivity Extensions for the coming 15/17 years. The Journal reviews issues that impact on all pivotal aspects of drug approval system with specific details for ANDA/AADAs NDAs and EU Dossiers including international perspectives on regulatory affairs. Features unique, authoritative **s**ide-**b**y-**s**ide comparisons, summaries and development drug checklists as a Journal specialty.

The *International Journal of Generic Drugs* provides a free exchange of scientific knowledge while promoting the generic and innovative pharmaceutical sciences. Selected papers, articles and reviews may be compiled by the publishers and incorporated after editing into the **24** volume authoritative **Handbooks of Pharmaceutical Generic Drug Development™** *series* with each volume, (updated twice annually), targeting in full details a specific dosage form. Reviews and papers are refereed, while scientific correspondence is subject to editorial oversight. Contributions to this Journal are published free of charge. The Journal is printed on acid-free paper (up to 60% recycle content) meeting ISO 9706, SFS 1083 and Nordic Environmental Standards of Certification.

The International Journal of Generic Drugs *and* Journal of Drug Development are the Official Journals of the International Association of Generic and Innovative Drug Manufacturers. Annual subscriptions rates for this Journal to non-members is US $285. Institutional rate is $330 by Air mail (Reduced rates are available to accredited members of the International Association of Generic and Innovative Drug Manufacturers - I.A.G.I.M. at $265 Print and $100 for the Electronic Edition) The Electronic Journal is available on disk, Locum Journal Navigator and subscribers of the Electronic *International Journal of Generic Drugs* (US $195) may have their subscription transmitted to their e-mail addresses. The subscription for Electronic multiple-users in large firms, universities or similar affiliations is $330. Electronic back order issues are $42 each (Print $48) The *International Journal of Generic Drugs* may be reviewed via the World Wide Web where the public may download a web-edition *Journal* in PDF™ Correspondence concerning editorial content addressed to: The Editor: The *International Journal of Generic Drugs* PO Box 874 Kochav Yair 44864 Israel. For correspondence concerning advertising matter address to the Advertising Manager: Fax:+972-97-494-532 E-mail: **journal@locumusa.com** Voice-mail: +972-97-494-965 Fax:+972-97-494-532 E-mail: **journals@locumusa.com** E-mail (sales): **info@locum.co.il**

Journal home page and archives may be viewed on Web Sites: http://www.locum.co.il
http://www.locumusa.com http://www.locumeuro.com

International Journal of Generic Drugs

ISSN 0793 694X - ISSN 0793 7784 - ISSN 0793 7822

Electronic Journal on Disk

Journal on the Web

e- Journal

ISSN 0793 7415 - 0793 7806

19 99

Manuscript Preparation & Submission: See end of this issue for Call for Papers and Notice to Authors.

For additional information, contact:- The Publications Department - Locum International Publishing House; PO Box 874, 50, Gilad Street, Kochav Yair, 44864 Israel. Fax: +972-97-494-532

E-mail : journal@locumusa.com

http://www.locumusa.com
http://www.locumeuro.com

Contributions to this journal are published free of charge and printed on acid-free paper

The *International* Journals & 24 volume Handbook *Series* are available from these appointed agents or subscription services world-wide:

SUBSCRIPTION AGENTS

Blackwell's Information Service (Readmore)
Corporate & Medical Specialists, 22 CORTLANDT STREET NEW YORK N Y 10007-3107 USA 1-800-221-3306
Fax: 212 233 0746 http://www.blackwells.com

BLACKWELLS PERIODICALS (Michelle Edney) B.H. Blackwells Ltd. PO Box 40 HythBridge Street OXFORD OX1 2EU ENGLAND +441865-792792 **F**ax+441865 791438 http://www.blackwell.co.uk

DA INFORMATION SERVICES PTY LTD. 648 Whitehorse Road Mitcham Victoria 3132 AUSTRALIA. +61-3-9210-7777
Fax:+61-3-9210-7788 http://www.dadirect.com.au
e-mail: service@dadirect.com.au

DAWSONS US 1001 West Pines Rd OREGON IL 61061-9570 USA 815-732-9001 **F**ax: 815-732-2123
e-mail: rates@faxon.com Toll Free: 1-800-852-7404

DAWSONS FRANCE Rue de la Prairie, Villebon-sur-Yvette, **91871 Palaiseau CEDEX** FRANCE Tel:33 1 69 10 47 00 Fax33 1 64 54 83 26
Email: ladeuille@dawson.co.uk

RoweCom 725 Concord Av. CAMBRIDGE MA 02138 USA. 1-800-633-6088 519-858-5105
Fax:519-858-5107 e-mail: inquiry@subscribe.com

EBSCO 1140 Silver Lake Road CARY IL 6013-1685 USA. 1-800-633-6088 847-639-2899
Fax:847-639-7514 e-mail: webmaster@ebsco.com

EBSCO 17-19 Washington Street TENAFLY AL 07670-2084 USA 205-991-6600 Fax:205-991-1234

The FAXON Company 15 South West Park Westwood MA 02090-1585 USA 617-329-3250 **F**ax: 617-329-9875

ROWCOM 1673 Richmond Street Suite 240 London ONTARIO CANADA 1-800-769-3266
Fax: 519-858-5107 e-mail: info@subscribe.com
http://www.rowe.com

SWETS & ZEITLINGER BV HEEREWEG 347 B 2161 CA LISSE P.O. Box 830 2160 SZ LISSE NETHERLANDS +31 252 435 111
Fax+31-252-415-888 e-mail: infoho@swets.nl
http://www.swets.nl

LAVOISIER ABONNEMENTS 14 Rue de Provigny 94236 CACHAN Cedex FRANCE. **F**ax: 33-1-47-40-67-03 33-1-47-40-67-00 e-mail: info@lavoisier.fr or abo@lavoisier.fr http://www.lavoisier.fr

KARGER LIBRI Peter Graben 31, PO Box CH 4009 BASEL SWITZERLAND 0241-4777-470
Fax: 0241-4777-479 e-mail: libri@libri.karger.ch
http://www.karger.ch/libri

MARUZEN Co Ltd. 3-10 NIHOMBASHI 2-CHROME CHUO-KU TOKYO 103 JAPAN
+81-3-3275-8591 **F**ax: +81-3-3275-1937

International Journal of Generic Drugs

ISSN 0793 694X - ISSN 0793 7784 - ISSN 0793 7822

Electronic Journal on Disk

Journal on the Web

e- Journal

ISSN 0793 7415

The *International Journal of Generic Drugs* is published every six to eight weeks in print and electronic formats.

Journal statistics:- The *International Journal of Generic Drugs* distribution stands at approximately +1900 to Universities, Institutional Organizations, Pharmaceutical Consultants, Generic Drug firms, and research-based pharmaceutical firms.

The Journal is distributed to over thirty five Regulatory Agencies in the Canada, Chile, China, European Union Countries (18), India, Taiwan, Japan, US, and the majority of the Pacific Rim countries.

A Word from Our Publishers

The *International Journal of Generic Drugs* is a leading pharmaceutical scientific journal. Peer reviewed by the Editorial Advisory Board, the journal offers a regular subscription via print, electronic diskette, Online or e-mail distribution. The journal is distributed in three geographic world zones. US/Canada issues - start at calendar year, Euro issues - start at mid-year and Pacific Rim issues - start at the academic year.

Electronic Journal-on-Disk

The Electronic *International Journal of Generic Drugs* is available on 3.5 Disk in Adobe's Portable Document Format (PDF™). The Acrobat Reader is a free reader and is available via our web sites linked direct to Adobe's site.
Full Yearly Volumes are available on CD. A complementary e-Journal may be requested via email (as an attachment).

Journal on the Web

The Electronic Web version of the *International Journal of Generic Drugs* may be reviewed or down loaded from any of the publishers' web sites at:-

- www.locum.co.il
- www.locumUSA.com
- www.locumEuro.com
- www.locumPacific.com (2000)

e- Journal

The Electronic *International Journal of Generic Drugs* is transmitted via the Internet to the subscriber's own e- address. This is faster to download than reviewing the ONLINE edition.
Complimentary e-mail issues are sent each month to international agency regulators and government departments.

The Journal

The *International Journal of Generic Drugs* printed edition is posted every six weeks to the subscriber's specified mailing address. (8 per annum, plus special supplements to IAGIM members).

International Journal of Generic Drugs

ISSN 0793 7784

Electronic Journal on Disk

Journal on on Web

e- Journal

ISSN 0793 7806

The International Journal of Generic Drugs is the Official Journal of the International Association of Generic and Innovative Drug Manufacturers. Annual subscriptions rates for non-members US $285. Institutional rate is $330 (Air mail) Reduced rates are available to accredited members of the International Association of Generic and Innovative Drug Manufacturers - I.A.G.I.M. at $265)

The Journal is published in print and electronic editions eight times per year in the following formats:

Euro - Print	ISSN 0793-7784
Euro - Electronic	ISSN 0793-7806

Editorial

19 Calendar 99

Vol. 03 - No 01

Ad Closing:	5 May. 1999
Materials:	8 May. 1999
Publishes:	30 May 1999

Vol. 03 - No 02

Ad Closing:	13 June 1999
Materials:	18 June 1999
Publishes:	9 July 1999

Vol. 03 - No 03

Ad Closing:	12 August 1999
Materials:	19 August 1999
Publishes:	25 August 1999

Vol. 03 - No 04

Ad Closing:	4 Sept 1999
Materials:	8 Sept 1999
Publishes:	25 Sept 1999

Vol. 03 - No 05

Ad Closing:	5 Oct. 1999
Materials:	10 Oct. 1999
Publishes:	25 Oct. 1999

Vol. 03 - No 06

Ad Closing:	01 Nov. 1999
Materials:	06 Nov. 1999
Publishes:	12 Nov. 1999

Vol. 03 - No 07

Ad Closing:	5 Dec. 1999
Materials:	6 Dec. 1999
Publishes:	10 Dec. 1999

Vol. 03 - No 08

Ad Closing:	10 Dec. 1999
Materials:	15 Dec. 1999
Publishes:	31 Jan. 2000

US & Canada - Print	ISSN 0793-694X
US & Canada - Electronic	ISSN 0793-7415
Euro - Print	ISSN 0793-7784
Euro - **Electronic**	ISSN 0793-7806
Pacific Rim - Print	ISSN 0793-7822
Pacific Rim - **Electronic**	ISSN 0793-7830

International Journal of Generic Drugs

ISSN 0793 694X - ISSN 0793 7784 - ISSN 0793 7822

Electronic Journal on Disk

Journal on the Web

e-Journal

ISSN 0793 7415

Publisher: PO Box 16075 Arlington VA 22215 USA

US Fax +(1)-435-808-1891

In This Issue

CONTENTS

Vol. 03 No.08 - 2000

journals@locumusa.com

journals@locumeuro.com

Publisher: PO Box 16075 Arlington VA 22215 USA

Issue - Highlights

REPRINT ISSUE ❖❖ REPRINT ISSUE

Printer: Locum Press St. Johns Wood London UK.

UK Fax: +(44)-207-900-2096

GUIDANCE FOR INDUSTRY

Impurities in Drug Substances

Draft Guidelines Revisited
First Issued June 1998
NO FINAL GUIDE YET

...in ANDAs

INTRODUCTION

Draft active drug substance guidance published back in June 1998 provide, draft recommendations for including information in abbreviated new drug applications (**ANDAs**) and supporting drug master files (**DMFs**) on the identification and qualification of **impurities in drug substances** produced by chemical syntheses for both monograph and non-monograph drug substances. Impurities in drug substances are addressed from two perspectives:

- CHEMISTRY ASPECTS

including classification and identification of impurities, generating analytical reports, setting specifications, and a brief discussion of analytical procedures

- SAFETY ASPECTS

including comparative studies and genotoxocity testing.

Evaluate & Compare Innovator Drug Impurities

Specific guidance is provided for:

- Qualifying impurities found in the drug substance used for the ANDA via a comparison with impurities found in the related USP monograph, scientific literature, or **innovator** material
- Qualifying impurities found at higher levels in the drug substance used for the ANDA than found in the related USP monograph, scientific literature, or **innovator** material;
- Qualifying impurities in the drug substance used for the ANDA that are **not** found in the related USP monograph, scientific literature, or **innovator** material;
- Threshold levels, below which qualification is not needed.

The June 1998 FDA draft guidance is not applicable to the following classes:-

- biological and biotechnological
- peptides,
- oligonucleotides
- radio-pharmaceuticals
- fermentation & derived semi-synthetic products
- herbal products
- crude products of animal/plant origin.

The recommendations in this guidance are effective upon publication of the *final* guidance (sometime in 2000) and should be followed in preparing new applications and supplements for changes in drug substance synthesis or process.

However, if the information in a drug substance **DMF** cited in such an ANDA or ANDA supplement has been reviewed prior to the publication of the *final* guidance, this guidance does not apply.

This guidance is intended to be a companion document to the International Conference on Q3A Harmonization (ICH) guidance.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

10 'RULES TO REMEMBER'

Rule No.1 - Evaluate the RLD impurity profile (i.e. get a baseline).

Rule No.2. Treat with CAUTION or REJECT a vendor profile HIGHER than the innovator material.

Rule No.3. LOOK at impurity profiles in the major pharmacopoeia (USP / BP / JP) and compare with vendor's dedicated synthesis (comparing profiles is important)

Rule No.4. 'Approved vendors' may have *unique* impurities due to the purifying process. LOOK for these 'specified impurities' in the actives chromatograms (i.e. "Stress the Active material").

Rule No.5. Unknown impurities must not exceed 0.1% (if they do, go back to active vendor to clean up material).

Rule No.6. Organic impurities are the main focus in impuritiy profiles (Note: residual solvents have there own guideline and limits).

Rule No.7. Do get the DMF holder to state the 'specific impurities' ***and*** the potential impurities (i.e. those impurities which ***do*** arise and those which ***can*** arise).

Rule No.8. Always stress the active *in-house* to see which impurities do occur.

Rule No.9. In drug development, if the active has an unknown >0.1% - and it can **not** be reduced - Look for an alternative supply with a better profile.

Rule No.10. REMEMBER an unknown impurity close to 0.1% may grow to >0.1% on stability (ageing). There's no such concept as a safe **unknown** >0.1%

Q3A Impurities in New Drug Substances.

[The ICH Q3A 27 guidance was published in the *Federal Register* on January 4, 1996 (61 FR 371), and issued as a Center for Drug Evaluation and Research (CDER) guidance.]

Evaluate this draft guidance side-by-side with Q3A

ICH Q3A provides recommendations for

(1) inclusion of information regarding specified impurities in certain **new** drug applications **(NDAs)** (identified and unidentified impurities in new drug substance specifications) and,

(2) qualification of impurities (the process of acquiring and evaluating data that establishes the biological safety of individual impurities or a given impurity profile at the level(s) specified).

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

Generic drugs are **not** covered by ICH Q3A. However, many of the recommendations in ICH Q3A are applicable to drug substances used in generic drug products. To provide, comparable processes for new and generic drug review, this guidance was developed using the ICH Q3A framework.

At a meeting held June 22, 1993, an FDA Ad Hoc Advisory Committee recommended that there should be a **0.1** percent threshold above which isolation and characterization of individual impurities should apply to chemically synthesized drug substances including drug substances used in generic drug products.

For compendial materials, the USP 23 in *General Notices and Requirements* (p. 7) states that it is manifestly impossible to include in each monograph a test for every impurity that may arise from a change in the source of material or a change in processing. Consequently, few USP monographs have acceptance criteria for individually identified impurities.

However, USP has adopted a **0.1** percent threshold for impurity identification via the publication of:- *Other Impurities* in *General Notices and Requirements*

(Sixth Supplement, p.3636), which became official on November 15, 1996.

CLASSIFICATION OF IMPURITIES

Impurities may be classified into the following categories:

- Organic Impurities (Process and Drug Related)
- Inorganic Impurities
- Residual Solvents

Organic impurities may arise during the manufacturing process and / or storage of the drug substance. They may be identified or unidentified, volatile or non-volatile, and include:

- Starting materials
- By-products
- Intermediates
- Degradation products
- Reagents, ligands, and catalysts

Inorganic impurities may derive from the manufacturing process. They are normally known and identified and include:

- Reagents, ligands, and catalysts
- Heavy metals
- Inorganic salts
- Other materials (filter aids, charcoal)

Residual solvents are organic or inorganic liquids (water) used during the manufacturing process. Since these are generally of known toxicity, the selection of appropriate controls is easily accomplished.

Excluded from this document are:

- Extraneous contaminants, which should not occur in drug substances and are more appropriately addressed as good manufacturing practice issues;
- Polymorphic forms, solid state property of the drug substance; and
- Enantiomeric impurities.

RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

A. ORGANIC IMPURITIES

The DMF holder *or* the applicant should summarise those actual and potential impurities most likely to arise during the synthesis, purification, and storage of the drug substance.

This summary should be based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

the impurity profile of the drug substance, and possible degradation products.

This discussion may include only those impurities that may *reasonably* be expected based on knowledge of the chemical reactions and conditions involved.

In addition, the DMF holder *or* the ANDA applicant should summarize the laboratory studies conducted to detect impurities in the **drug substance**.

Obtain Drug Substance Impurities Report from DMF Holders

This summary should include
(a) test results of materials manufactured during the development process **and** batches from the proposed commercial process, as well as,
(b) results of intentional degradation studies used to identify potential impurities that arise during storage.

Assessment of the proposed commercial process may be deferred until the first batch is produced for marketing.
The impurity profile of the drug substance lots intended for marketing should be compared with those used in development and any differences discussed.

The studies (e.g., NMR, IR, and MS) conducted to characterize the structure of actual impurities present in the drug substance at or above an apparent level of **0.1** percent (e.g., calculated using the response factor of the drug substance) should be described.

Note that all recurring impurities at or above an apparent level of **0.1** percent (see analytical procedures) in batches manufactured by the proposed commercial process should be identified.

Degradation products observed in stability studies at recommended storage conditions should be similarly identified.

Impurity Profile Summary

When identification of an impurity is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the DMF or application. Where attempts have been made to identify impurities below the 0.1 percent level, it is useful to also report the results of these studies.

Summaries of Un-identifiable Drug Substance Impurities are required from DMF Holders

Identification of impurities below apparent levels of **0.1** percent is generally **not** considered necessary.
However, identification should be attempted for those potential impurities that are expected to be unusually potent, producing toxic or pharmacologic effects at a level lower than 0.1 percent.

In all cases, impurities should be qualified as described later in this guidance.

Do not round impurity assays up to 0.1%

Although it is common practice to round analytical results of between 0.05 and 0.09 percent to the nearest number (i.e., 0.1 percent), for the purpose of this

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

guidance, such values should not be rounded to 0.1 percent in determining whether to identify the impurities.

B. INORGANIC IMPURITIES

Inorganic impurities are normally detected and quantitated using pharmacopoeial or other appropriate procedures. Carry-over of catalysts to the drug substance should be evaluated during development. The need for inclusion or exclusion of inorganic impurities in the drug substance specifications should be discussed.

Acceptance criteria should be based on pharmacopoeial standards or known safety data.

C. RESIDUAL SOLVENTS

The control of residues of solvents used in the manufacturing process for the drug substance should be discussed. Any solvents that may appear in the drug substance should be quantified using analytical procedures with an appropriate level of sensitivity. Pharmacopoeial or other appropriate procedures should be used.

Acceptance criteria should be based on pharmacopoeial standards or known safety data taking into consideration dose, duration of treatment, and route of administration. Particular attention should be given to quantitation of toxic solvents used in the manufacturing process as described in the ICH guidance *Q3C Impurities: Residual Solvents.*

ANALYTICAL PROCEDURES

The **DMF** *or* abbreviated application should include documented evidence that the analytical procedures are validated and suitable for the detection and quantitation of impurities.

Differences in the analytical procedures used during development and proposed for the commercial product should be discussed in the **DMF** or abbreviated application.

Organic impurity levels can be measured by a variety of techniques, including those that compare an analytical response for an impurity to that of an appropriate reference standard or to the response of the drug substance itself.

Reference standards used in the analytical procedures for control of impurities should be evaluated and characterized according to their intended uses.

It is considered acceptable to use the drug substance to estimate the levels of impurities when the response factors of the drug substance and impurities are close. In cases where the response factors are not close, this practice may still be acceptable, provided a correction factor is applied or the impurities are, in fact, being overestimated. Analytical procedures used to estimate identified or unidentified impurities are often based on analytical assumptions (e.g., equivalent detector response). These assumptions should be discussed in the **DMF** submission or abbreviated application.

REPORTING IMPURITY CONTENT OF BATCHES

Analytical results should be provided for all batches of the drug substance used for stability testing, as well as for batches representative of the proposed commercial process. The content of individual impurities, both identified and unidentified, and total impurities observed in these batches of the drug substance should be reported with the analytical procedures indicated.

A tabulation (e.g., spreadsheet) of the data is recommended. Impurities should be designated by code number or by an appropriate descriptor, for example, name or retention time. Levels of impurities that are present but are below the validated limit of quantitation (LOQ) need not be reported.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

If analytical procedures change during development, reported results should be linked with the procedure used and appropriate validation information should be provided.

Representative chromatograms should be provided.

Chromatograms of such representative batches, from methods validation studies showing separation and detectability of impurities (e.g., on spiked samples), along with any other impurity tests routinely performed, can serve as the representative impurity profiles.

The applicant or DMF holder should ensure that complete impurity profiles (i.e., chromatograms) of stability batches are available if requested.

A tabulation should be provided comparing impurity levels between stability and other batches.

- For each batch of the drug substance, the report should include:
- Batch identity and size
- Date of manufacture
- Site of manufacture
- Manufacturing process
- Impurity content, individual and total
- Use of batches
- Reference to analytical procedures used

ACCEPTANCE CRITERIA FOR IMPURITIES

The specification for a drug substance should include acceptance criteria for impurities.

Stability studies, chemical development studies, and routine batch analyses can be used to predict those impurities likely to occur in the commercial product.

The selection of impurities to include in the drug substance specification should be based on the impurities found in the batch(es) manufactured by the proposed commercial process.

Those impurities selected for inclusion in the specification for the drug substance are referred to as *specified impurities* in this guidance.

Specified impurities may be identified or unidentified and should be individually listed in the drug substance specification (see below). A rationale for the inclusion or exclusion of impurities in the specification should be presented.

This rationale should include a discussion of the impurity profiles observed in batches under consideration, together with a consideration of the impurity profile of material manufactured by the proposed commercial process.

Specific identified impurities should be included along with recurring unidentified impurities estimated to be at or above 0.1 percent.

For impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation / detection limit of the analytical methods should be commensurate with the level at which the impurities need to be controlled.

For unidentified impurities, the procedure used and assumptions made in establishing the level of the impurity should be clearly stated.

Unidentified impurities included in the specification should be referred to by some appropriate qualitative analytical descriptive label (e.g., "unidentified A," "unidentified with relative retention of 0.9").

Finally, a general acceptance criteria of not more than 0.1 percent for any unspecified impurity should be included. Acceptance criteria should be set no higher than the level that can be justified (see the *Impurities Decision Tree* for generic drugs, Attachment I) either by

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

comparative studies or genotoxicity studies, and unless such data indicate otherwise, no lower than the level achievable by the manufacturing process and the analytical capability.

In other words, where there is no safety concern, impurity acceptance criteria should be based on data generated on actual batches of the drug substance allowing sufficient latitude to deal with normal manufacturing and analytical variation, and the stability characteristics of the drug substance.

Erratic batch-to-batch impurity levels may indicated incomplete validation

Although normal manufacturing variations are expected, significant variation in batch-to-batch impurity levels may indicate that the manufacturing process of the drug substance is not adequately controlled and validated.

In summary, the drug substance acceptance criteria should include, where applicable, acceptance criteria for:

- **Organic Impurities:**
  - Each specified identified impurity
  - Each specified unidentified impurity at or above 0.1 percent
  - Any unspecified impurity, with a limit of not more than 0.1 percent
  - Total impurities
- **Residual Solvents**
- **Inorganic Impurities**

A summation of assay value and impurity levels generally may be used to obtain mass balance for the test sample. The mass balance need not add to exactly 100 percent because of the analytical error associated with each analytical procedure.

Mass Balances may exceed 100% due to analytical variance

The summation of impurity levels plus the assay value may be misleading, for example, when the assay procedure is non-specific (e.g., potentiometric titrimetry) and the impurity level is relatively high.

Unknown Peaks must not exceed 0.1% of the Labelled amount

QUALIFICATION OF IMPURITIES

Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

The DMF holder or the applicant should provide a rationale for selecting impurity acceptance criteria based on safety considerations.

The level of any impurity present in a drug substance that is in compliance with a USP specification or has been adequately evaluated in comparative or in vitro genotoxicity studies or has been evaluated via an acceptable *Quantitative Structure Activity Relationships* (QSAR) database program is considered qualified for ANDAs.

Note: Impurities that are also significant metabolites do not need further qualification.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

If data are not available to qualify the proposed acceptance criteria of an impurity, studies to obtain such data may be needed when the usual qualification threshold levels given below are exceeded:

Maximum Daily Dose	Qualification Threshold
≤2g/day	0.1% or 1 mg per day (lowest value)
>2g/day	0.05%

Higher or lower threshold levels for qualification of impurities may be appropriate for some individual drugs based on scientific rationale and level of concern, including drug class effects. For example, qualification may be especially important when there is evidence that such impurities in certain drugs or therapeutic classes have previously been associated with adverse reactions in patients. In these instances, a lower qualification threshold level may be appropriate.

Technical factors (manufacturing capability and control methodology) may be considered as part of the justification for selection of alternative threshold levels. Proposals from applicants for alternative threshold levels will be considered by the FDA on a case-by-case basis

BPC Manufacturers should decrease the impurity below the maximum level

The Impurities Decision Tree for generic drugs (below) describes considerations for the qualification of impurities when thresholds are exceeded. In some cases, decreasing the level of impurity below the threshold, rather than providing additional data, may be the simplest course of action. Alternatively, adequate data may be available in the scientific literature to qualify an impurity.

The studies that should be performed to qualify an impurity will depend on a number of factors, including the patient population, daily dose, and route and duration of drug administration.
Such studies are normally conducted on the drug substance containing the impurities to be controlled, although studies using isolated impurities are acceptable.

Levels L1 through L4 are recommendations for the type of information that would be considered to provide assurance that the impurity in question is "innocuous by virtue of having no significant, undesirable biological activity in the amounts present" (see USP <1086> *Impurities in Official Articles*).

Only in Level L5, where concern regarding possible toxicity is indicated, is additional testing recommended (e.g., by a battery of in vitro genotoxicity tests).

Level L6 would be for those rare instances where an impurity has not been qualified. In such cases, the ANDA would then fall outside the purview of section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act). Additional clarification regarding the levels in the Impurities Decision Tree for Generic Drugs is provided.

First level (L1):

This level evaluates whether the impurity in question is "above threshold"? See the threshold table. (This level is identical to the corresponding level in the ICH *Decision Tree for Safety Studies*.)

Second Level (L2):

This level evaluates whether the "structure is elucidated?" This refers to structural identification or characterization exactly as in the ICH Decision Tree for Safety Studies.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

However, in those rare cases where it is not possible to identify the impurity by structure, the efforts made should be satisfactorily documented. Once the impurity has been structurally identified, one could go to level L3.

Five of the Six impurity levels impact on ANDAs

Third Level (L3**a**):

Compliance with a USP acceptance criteria for a known individual impurity (e.g., see impurity listed in the Clidinium Bromide USP monograph).

Third Level (L3**b**): A comparison of the impurity profile of the generic drug substance with the process impurities profile on an average of three or more different lots of the innovator's drug product is recommended.

This comparative study should be performed using appropriate discriminating analytical tests such as HPLC or Capillary Electrophoresis.

Evaluate 3 or more innovators lots to establish ANDA's Impurity baseline

The impurity is qualified if it is found at similar levels (no more than two-fold higher for most drug substances).

Two-fold higher criteria are justified for several reasons. For example, the innovators' impurity acceptance criteria are set higher than levels observed in drug substances, and the safety studies that qualified the innovators' drug substances are carried out at significantly higher levels than the specifications agreed to under FDA's pharmacology and toxicology evaluations.

Unidentified impurities present in both innovator & generic are deemed acceptable

In certain dosage forms where sensitivity concerns arise, the impurity levels should be no higher than the innovator's level for toxic impurities.

In generic drugs, an unidentified impurity may still be considered qualified in cases where the impurity is observed at similar levels in the innovator's product via a comparative study.

Third Level (L3c):

This level looks at an impurity at a "higher level, or a different new impurity."

New means one that was not previously seen in the bulk drug substance. The level of the new impurity may be qualified from the scientific literature if it is substantiated that this impurity is an *ordinary impurity* (see USP <1086>) at the levels used.

The scientific literature would include recognized scientific publications. Alternatively, the new impurity may be qualified by lowering it to below the ICH threshold level, or by following the next level in the Impurities Decision Tree for generic drugs.

Fourth Level (L4):

Is the impurity "related to others with known toxicity"? As one approach, the use of a *Quantitative Structure Activity Relationships* (QSAR) database program may be helpful in identifying whether an impurity is related to others of known toxicity. The use of such a program is acceptable to the Office of Generic Drugs (OGD).

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

Levels 1 to 4 evaluate drug safety aspects

Modules currently recommended are: *Rodent Carcinogenicity, Developmental Toxicity Potential, Ames Mutagenicity* (five strains), and for topicals, *Skin Sensitization*.

If no potential for concern is indicated by QSAR evaluation, the impurity is considered qualified, but it should not exceed a level of 0.5 percent or 500 micrograms per day, whichever is less (equivalent to 0.5 percent of 100 mg of a drug substance), without other supporting data (such as genotoxicity test data).

A determination to accept the data will be made on a case-by-case basis taking into consideration the therapeutic use of the drug product, its intended duration of administration, and the results of the QSAR analysis.

However, if the QSAR evaluation does not provide sufficient information because the program cannot perform the evaluation due to the lack of relevant information in the database, the manufacturer should lower the impurity level to below the ICH threshold or qualify the new impurity at the L5 level.

Fifth Level (L5):

This level describes evaluation of the toxicity of an impurity via a battery of in vitro genotoxicity tests

Wherever possible the onus is on BPC manufacturer to lower or remove the offending impurity

(See the ICH Decision Tree for Safety Studies regarding genotoxicity studies).

If the result of genotoxicity testing raises a concern, the need for additional toxicity testing will be evaluated on a case-by-case basis.

Factors to be considered include the therapeutic use of the drug product, its intended duration of use, and results of the QSAR analysis.

However, even in those cases where no potential for concern is indicated by the genotoxicity testing, the need for further toxicity testing should be evaluated if the impurity level exceeds either **1** percent of the drug substance or **1** mg/day, whichever is lower, at the human therapeutic dose of the drug product.

If toxicity issues are confirmed by these in vitro tests, the **DMF** holder or applicant may either purify the drug substance to reduce the impurity to a level below the ICH threshold or go to the next level (L6) in the Impurities Decision Tree for generic drugs.

Six Level (L6):

Animal Toxicity testing

This level involves qualification of the impurity "by general toxicity testing" If this pathway is used, the ANDA would fall under section 505(b) of the Act.

General toxicity testing involves animal testing, thus an application would not be deemed acceptable by OGD under section 505(j) of the Act.

Level Six

Impurity Testing violates the ANDA submission status

The drug substance manufacturer as well as the applicant should be cognisant of this issue before the applicant commits to extensive studies with the bulk drug substance.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

NEW IMPURITIES

During the course of a drug development program, the qualitative impurity profile of the drug substance may change or a new impurity may appear, for example, as a result of synthetic route changes, process optimization, or scale-up.

The impurity package depends on the synthesis route

New impurities may be identified or unidentified. Such changes call for consideration of the need for qualification of the level of the impurity unless it is below the threshold values as noted above.

Unidentified
below the level
Identified
above the level

When a new impurity exceeds the threshold, the Impurities Decision Tree for generic drugs should be consulted. Studies should compare the drug substances containing a representative level of the new impurity with previously qualified material, although studies using the isolated impurity are also acceptable.

Do's & Don'ts

Do establish all the potential impurities that can arise from the approved manufacturers (suppliers) synthesis pathway.

Do collaborate with the approved supplier on which residual impurities actually remaining in the active drug substance.

Don't qualify an impurity if it can be removed from the active material.

Don't exceed the RLD's impurity levels.

Don't test for other synthesis pathway impurities

Glossary of Terms

Acceptance Criteria:
Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.

Chemical Development Studies:
Studies conducted to scale-up, optimize, and validate the manufacturing process for a drug substance.

Drug Substance:
The designated therapeutic moiety. See also the definition in 21 CFR 314.3.

Enantiomers:
Compounds with the same molecular formula as the drug substance, which differ in the spatial arrangement of atoms within the molecule and are non-superimposable mirror images.

Extraneous Substance:
An impurity arising from any source extraneous to the manufacturing process.

Genotoxicity Tests:
Genotoxicity tests can be defined as in vitro tests designed to detect compounds that induce genetic damage directly or indirectly by various mechanisms. (Compounds which are positive in tests that detect such kinds of genetic damage have potential to be human carcinogens and/or mutagens, i.e., may induce cancer and/or heritable damage.)

Herbal Products:
Medicinal products containing, exclusively, plant material and/or vegetable
drug preparations as active ingredients. In some traditions, materials of inorganic or animal origin may also be present.

Identified Impurity:
An impurity for which a structural characterization has been achieved.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

Impurity:
Any component of the drug substance that is not the chemical entity defined as the drug substance.

Impurity Profile:
A description of the identified and unidentified impurities present in a drug substance.

Intermediate:
A material produced during steps of the synthesis of a drug substance that must undergo further molecular change before it becomes the drug substance.

Ligand: An agent with a strong affinity to a metal ion.

Mass Balance:
The process of adding together the assay value and levels of degradation products to see how closely these add up to 100 percent of the initial value, with due consideration of the margin of analytical precision.

New Drug Substance:
The designated therapeutic moiety that has not been previously registered in a region or member state (also referred to as a new molecular entity or new chemical entity). It may be a complex, simple ester, or salt of a previously approved drug substance.

Polymorphism:
The occurrence of different crystalline forms of the same drug substance.

Potential Impurity:
An impurity that, from theoretical considerations, may arise from or during manufacture. It may or may not actually appear in the drug substance

Qualification:
The process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

Quantitative Structure Activity Relationship (QSAR):
Used for rationalization and prediction of in vivo mammalian toxicity of chemicals on the basis of their overall and/or local properties, as defined by their chemical structure and evaluated by using an appropriate data base and modules.

Reagent:
A substance, other than a starting material or solvent, that is used in the manufacture of a drug substance.

Safety Information:
The body of information that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

Solvent:
An inorganic (i.e. water) or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a drug substance.

Specification:
A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use.

Conformance to Specification:
Conformance to specifications means that the drug substance and/or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

Specifications are binding quality standards that are agreed to between the appropriate governmental regulatory agency and the applicant.

Specified Impurity:
An identified or unidentified impurity that is selected for inclusion in the drug substance specifications and is individually listed and limited in order to assure the safety and quality of the drug substance.

Starting Material:
A material used in the synthesis of a drug substance that is incorporated as an element into the structure of an

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

intermediate and/or of the drug substance.

Starting materials normally are commercially available and of defined chemical and physical properties and structure.

Toxic Impurity:

Impurities having significant undesirable biological activity.

Unidentified Impurity:

An impurity that is defined solely by qualitative analytical properties (e.g., chromatographic retention time).

Validated Limit of Quantitation:

For impurities at a level of 0.1 percent, the validated limit of quantitation should be less than or equal to 0.05 percent. Impurities limited at higher levels may have higher limits of quantitation

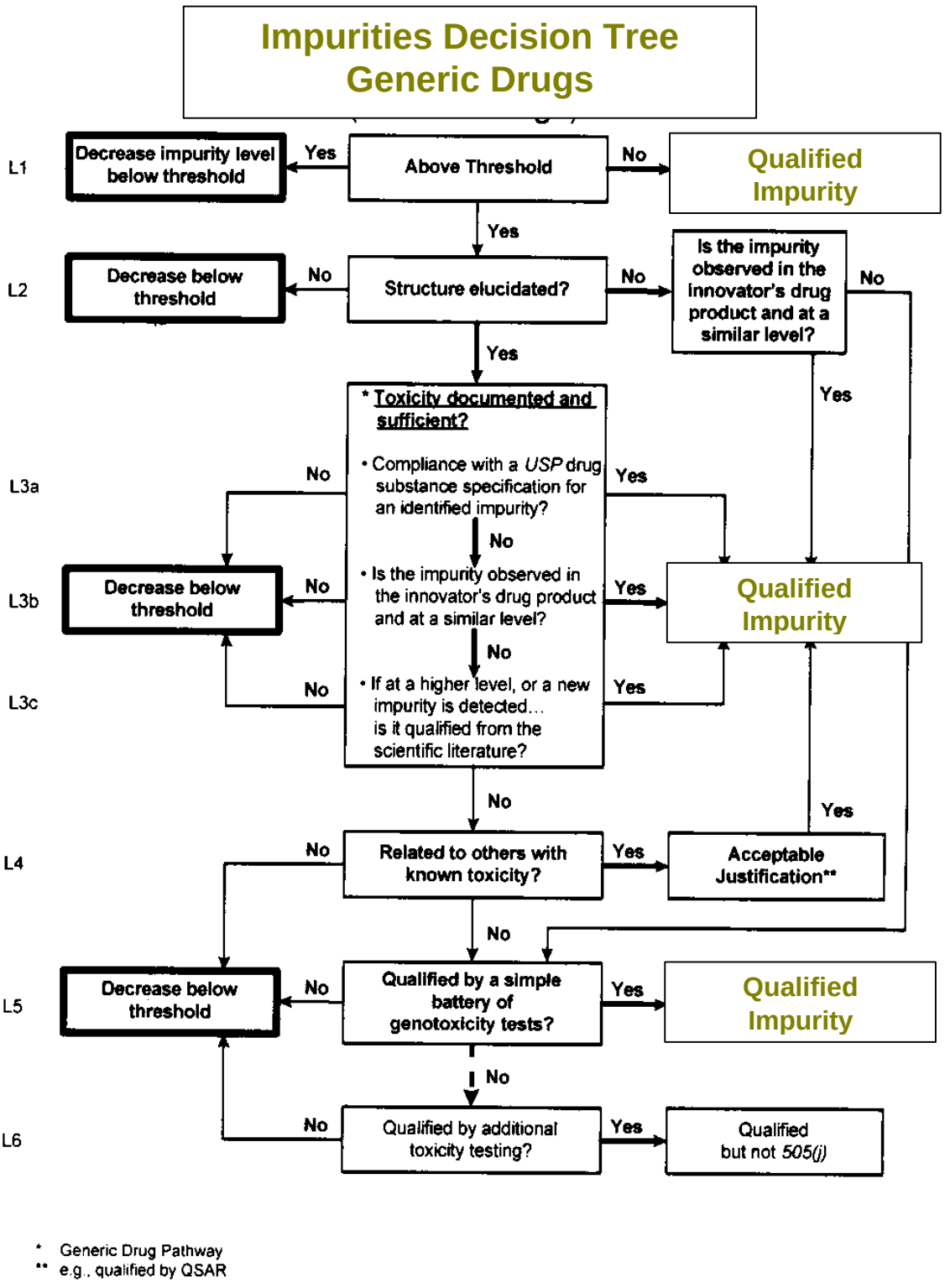
The definition of an impurity for an active drug **substance** includes water

The definition of an impurity for an **drug product** excludes water

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

(No Change in DRAFT GUIDANCE as of Jan 2000)

Impurities in Active Drug Substances



* Generic Drug Pathway
** e.g., qualified by QSAR

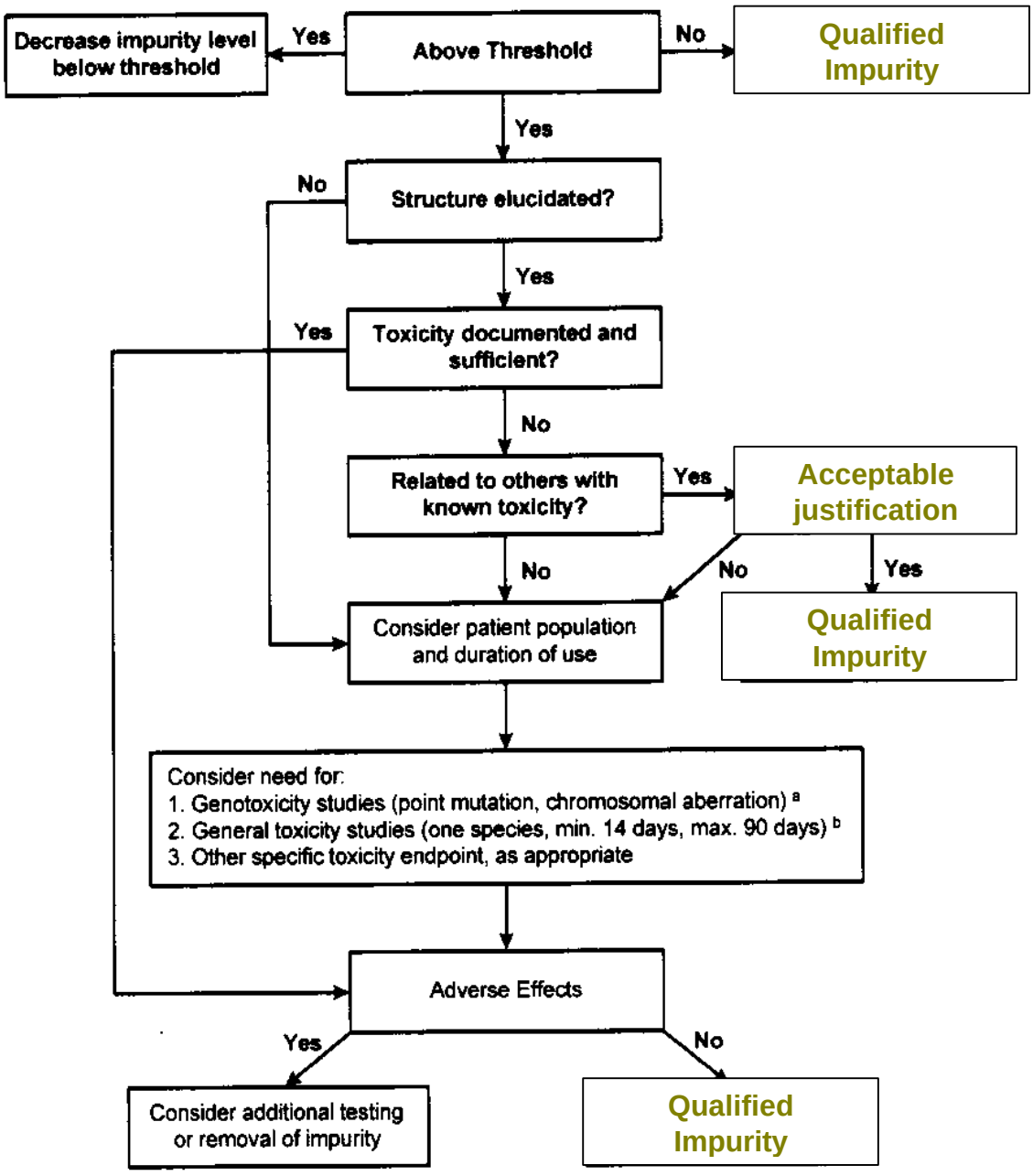
For Level 6 qualification go to ICH decision tree for additional Safety Studies [The need to go to level six (additional safety studies) **immediately disqualifies** active material for ANDA use]

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

(No Change in DRAFT GUIDANCE as of Jan 2000)

Impurities evaluation in Active Drug Substances

ICH DECISION TREE FOR SAFETY STUDIES



[a] If considered desirable, a minimum screen for genotoxic potential should be conducted. A study to detect point mutations and one to detect chromosomal aberrations, both in vitro, are seen as an acceptable minimum screen.

[b] For NDAs, if general toxicity studies are desirable, study(ies) should be designed to allow comparison of unqualified to qualified material. The study duration should be based on available relevant information and performed in the species most likely to maximize the potential to detect the toxicity of an impurity. In general, a minimum duration of 14 days and a maximum duration of 90 days will be acceptable.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

Swelling Matrix Dosage Form
- choice of releasing controlling excipients

'...Each release controlling agent must play its role - and all excipients must be absolutely necessary...'

CONTROLLING EXCIPIENTS

Non active ingredients used in modified release (MR) solid oral dose preparations are initially classified as to whether the non-active is a releasing or non-releasing controlling excipient. These excipient polymer materials are required to meet specific physical characteristics such as the ability to absorb gastric fluids or water.

Release controlling excipients

Release controlling excipients are inactive ingredients in the final dosage form that function *primarily* to extend the release of the embedded active drug substance. The release rate is defined as the amount of drug released per unit time when measured in an invitro dissolution testing apparatus or via an invivo correlation or bioequivalency test.

The release controlling excipient matrix may be incorporated into various modified or controlled release systems. The term MR (ER or CR) is used when the drug acts predominantly in the upper GIT and Delayed Release (DR) when active release is in the intestinal region via enteric coating of the dosage form.

Various Release mechanisms exist - all achieving a controlled and reproducible drug delivery from:-

- Bioerodible Matrix Systems
- Diffusional Controlled Systems
  - Matrix
  - Reservoir
- Dissolution controlled pulse-delivery
- Osmotic Controlled Systems
  - Core -no bag (Osmotic pump)
  - Core with bag (Osmotic pump)

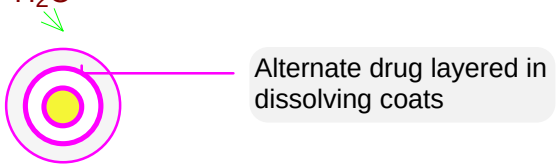
Non-releasing controlling excipients

These are inactive ingredients in the final dosage form that do not *significantly* effect the release of the active drug substance from the release matrix or controlled system. Colloidal Silicon Dioxide NF Magnesium Stearate NF are typical examples.

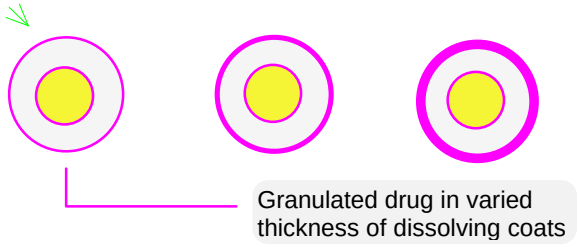
Critical Process Variables:

A specific processing step or a unit process that affects the dissolution performance and drug release from…

DISSOLUTION CONTROLLED PULSE DELIVERY

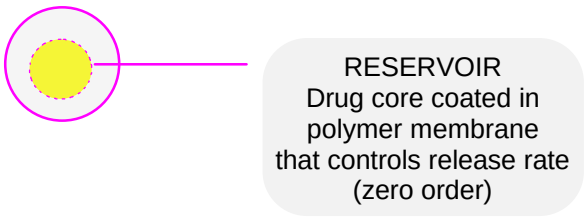


DIFFUSIONAL CONTROLLED SYSTEMS - MATRIX

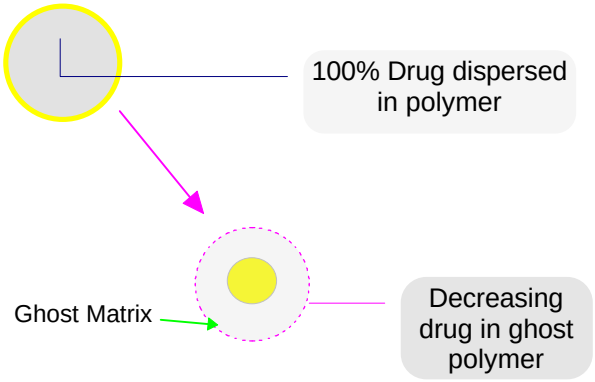


ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

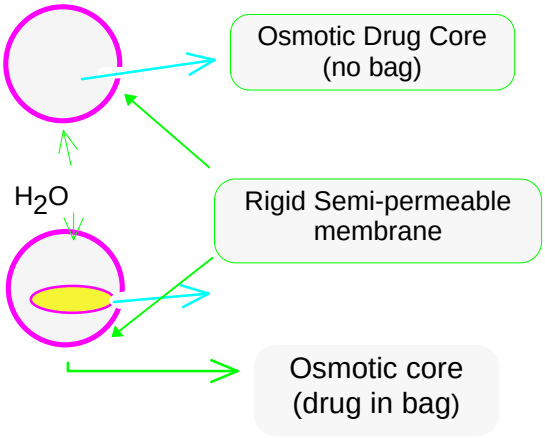
DIFFUSION CONTROLLED SYSTEMS - RESERVOIR



DIFFUSION CONTROLLED SYSTEMS - MATRIX with ghost



OSMOTIC CONTROLLED SYSTEMS



…the controlled formulation are termed **critical process variables** and are as important as the release controlling excipients. Examples are;

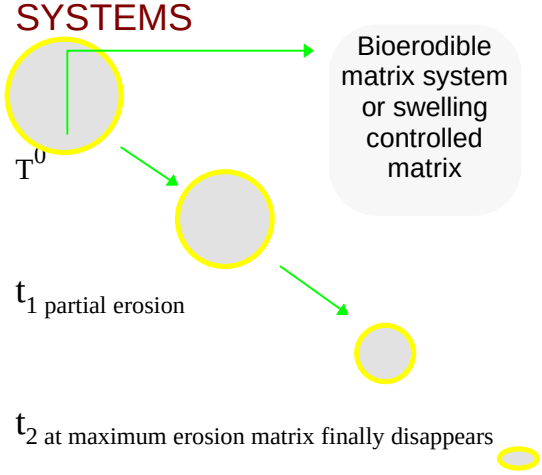
(a) particle size reduction of active material.

(b) Coating concentrations

(c) Thickness of erodible or diffusional coats and films

(d) Tablet hardness.

BIOERODIBLE MATRIX SYSTEMS



Drug Release from Erodible ER Tablets

Mode of action.

Hydrophilic matrixes consist of a drug in, *and* compressed with, a hydrophilic polymer. When these systems are placed in GI fluids or water, they start swelling and the tablet thickness increases.

Soon thereafter, polymer erosion and drug dissolution starts occurring together. In the majority of drug/polymer preparations, active drug is embedded (by standard granulation techniques) into the polymer matrix.

Active drug is released in the gastrointestinal tract via contributions from different release mechanisms. Initially surface erosion of the tablet face occurs and water imbibes into the polymer matrix.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

Slow direct erosions of the polymer matrix and erosion, after transient swelling, at the surface with the formation of a gel layer occur. Diffusion release of the drug from the polymeric matrix results, through the swelling gel layer, with concomitant ongoing polymer surface erosion. At the end of the drug release, the matrix is completely dissolved, suggesting that the overall drug release time is controlled by the tablet erosion.

Different polymer compositions bring about different degrees of drug retardation or enhancement, which may then be fine-tuned by varying the amount of additional ingredient components such as plasicizers (HPC) and matrix modifiers (PEGs). Release characteristics are mainly governed by the polymer / ingredient drug embedded matrix.

Modified HPMC Formulas.

Excipients are chosen either as release controlling excipients (RCE) or non release controlling excipients (NRCE).

Typical control release / extended release ingredients in swelling bioerodible matrix formulations are found as follows.

A swelling matrix that consists of hydroxypropyl methylcellulose (HPMC) in two distinct forms.

The unmodified excipient as a standard compendial HPMC (of say, viscosity value I).

The *modified* HPMC (of viscosity value II) as a standard compendial HPMC which has been modified through wet granulation with an appropriate film modifier **and** plasicizer.

These are the two release controlling excipients of the formula existing as two separate parts that will eventually be granulated together with the active material. When granulated together

they form a polymeric matrix. In the GIT this polymer matrix undergoes:

- surface wetting (rapid)
- surface swelling (slow process)
- surface erosion (ongoing)
- surface gel formation (ongoing)
- gradual inner polymer swelling
- ongoing outer gel erosion

OVERALL DRUG TRANSPORT

Drug molecules are released at the surface, as well as diffusing into the inner swelling polymer (a dissolution process) and then diffusing outwards through the swelling polymer and finally through the outer gel layers…

Povidone USP -

(non- release controlling excipient).
PVP K-30 is a preferred water soluble granulating agent. It may be used as an aqueous binder for the release controlling excipients. PVP K-90 normally produces harder granulates especially in HPMC//modified-HPMC formulations while combinations of PVP K-30 / PVP K-90 intra- and extra-granularly may be used to fine-adjust the dissolution rate, with the purpose of mimicking the innovator's product.

Colloidal Silicon Dioxide NF

(non- release controlling excipient)
used as a glidant, it promotes granulate flow by reducing of the inter-particulate friction. It is generally used extra-granularly in the formula at the final dry blending stage (Y-cone stage). Usual target amounts for solid oral dosage forms 0.5% - 3.0%. Controlled Release dosage forms use less about 0.33% - 1.0%.

Sodium Starch Glycolate NF

(non- release controlling excipient)
Intra- and extra-granular disintegrant promotes granulate flow and enhances granule disintegration. May be used to offset the initial hydrophobic effect of alkali lubricants in immediate release dosage forms.
As an extra-granular disintegrant (added at the final Y-cone stage) it is used in the end process dry mix extra-granularly with

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

the glidant and gives rise to rapid dosage form disintegration. NMT 5.0%, target 1.0 - 4.0%. Intra-granular incorporation tends to disintegrate the granule too rapidly and enhances the dissolution profile (promotes rapid dissolution).

Magnesium Stearate NF - (non- release controlling excipient)

The excipient is used us a lubricant. Lubricants are primarily used to prevent powder from sticking to the tablet tooling and to reduce the friction between the die wall and the tablet as it is being ejected. Usual target amounts for solid oral dosage forms including controlled release forms is around 0.5% - 1.0%. A minimum of dry blending is required (in the final stage blending.)

Hydroxypropyl Methylcellulose USP, Hydroxypropyl Cellulose NF

HPMC//modified-HPMC formulations comprise of wet granulating HPMC with a modified pre-granulated HPMC. The unmodified and modified HPMC components forms the basis of the release controlling excipients in bioerodible swelling matrices. Various viscosity grades of HPMC are available. (methocel™ K100LV;K4;E5)

These well known compendial controlled release excipients are capable of producing a slowly swelling, bioerodible matrix, in an extended release dosage form. The release rate can be adjusted up to 16 - 20 hours. The ratio of HPMC to Modified-HPMC used, normally ranges from 1:1, 2:1 to 3:1

Ratios of 75 HPMC : 25 HPMC (modified) are excellent starting points for development and generally, the total HPMC content constitutes approximately 1/3 to ½ of the overall tablet weight. The actual amount depends on of quantity of active material in the CR dosage form.

In HPMC//modified-HPMC controlled formulae the most practical approach is to choose the appropriate ratios and viscosity grades of the HPMC for the modified **and** unmodified portion via repeated dissolution testing of small development batches

Normally two different grades of HPMC USP/NF are granulated together.

HPC or MHEC are used as the matrix swelling modifiers, affecting both dissolution and diffusion (generally used in smaller amounts ranging from 2-10%) and may be formulated in conjunction with a variety of low M.W. plasticisers (Low molecular weight grades of polyethylene glycols (PEG 4000) / carbowaxes; or propylene glycol or even triacetin.)

Carbomer 934P NF. - (Release controlling excipients.)

Modifies bioerodible HPMC matrix component - both as a matrix component modifier and a plasticiser for swelling (diffusion and dissolution) controlled release matrix systems. The carbowaxes normally do not exceed 1% - 10% in CR HPMC/ modifiedHPMC formulations. Target levels chosen 0.75% -1.0% of the overall formula and 2-4% of the modified cellulose derivative.

Coating Ingredients - Standard Opadry™ formula are used, obtainable from Colorcon®. Contains Hydroxypropyl Methylcellulose NF as major components of the aqueous film coat. Highly compatible with HPMC / HPC formulations.

Excipient exposure

For ANDA submissions, the excipient should appear in the FDA's Inactive Ingredient Guide (IIG). This guide lists inactive ingredients that have been safely used in currently marketed OTC and prescription drug products for a specific route, in this case for oral use.

The second condition for the non active ingredient is that the percentage amount used in the product formula should not exceed the maximum percentage for the specific route (e.g. oral use) as stated in the Inactive Ingredient Guide.

The maximum quantity of a specific non active ingredient is generally determined by the FDA as the highest amount of non active that is currently approved for an OTC or ANDA product for *that* specific dosage form or route of administration.

ANDA approvals may be OTCs or prescription products. The above FDA internal rule apply only to ANDA submissions and do not apply to OTC non-ANDA products.

Choosing non-active excipients

Excipient-to-excipient interactions (color effects and incompatibilities) must be excluded. Uniformity of Content for granule and tablet may be impacted by the physical specifications of the excipients.

Generic manufacturers who evaluate the reference listed drug (RLD) and design a Q&Q formula may minimize fluctuations in dissolution and bioequivalent testing.

General Excipient Rules:

The non-active should ideally be compendial (USP/NF; BP; EP; JP etc.)

- The non-active should ideally be in the Handbook of Pharmaceutical Excipients (current 2nd Edition)
- The non-active should be in the FDA's IIG-Inactive Ingredient Guide regarding

⇒ same dosage route only

⇒ maximum percentage not exceeded.

- If the non-active is for an OTC tablet product *only* (not an ANDA) then it should be at least in the GRAS. lists.
- It is strongly recommended that non-actives selected for ANDA formula are subject to *approved supplier* procedures that is similar to Active Ingredients.

Inactive ingredients specifications

Inactive ingredients with unspecified physical size parameters may require quality control in two critical physical specifications (e.g. Magnesium stearate)

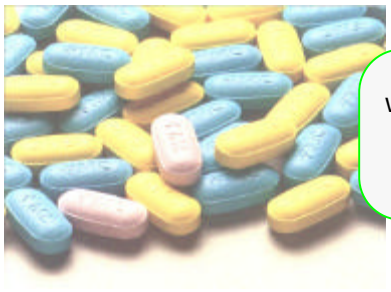
- ◊ particle size specification
- ◊ bulk density specification

Uniformity of Content-Granulate studies

It is important that generic manufacturers correlate excipient specifications and evaluate the impact on the bulk granulate 'uniformity of content' assay during in-process manufacture. Lubricated and un-lubricated granulation studies evaluating Content Uniformity and dissolution are recommended. **S**pecifications for particle size and bulk density ranges should be clearly specified in order to prevent significant differences (< 5%) in batch-to-batch and intra-batch dissolution assay values.

ERODIBLE ER TABLETS

(General scheme)



RSD = Relative Standard Deviation

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

Formula polymers are modified where drug SOLUBILITY changes i.e.:

- Freely soluble actives
- slightly soluble actives.

Dissolution curves for Verapamil SR produce a sustained release of 8 hours with the following dissolution profile

240 mg Dissolution Tolerances

Hours	Amount Dissolved %
1 (HCl)	8-20
2 (SGF)	15-35
3.5 (SGF)	35-65
5 (SGF)	55-85
8 (SGF)	>80

Pharmacopeial Forum Vol. 21, No 6

VERAPAMIL 240 mg SR Tablets

(using modified hydroxypropyl cellulose[1])

HPC wet granulated with Plasicizer (3% lecithin) Modifier added for fine tuning

HPMC (39%)

Modified HPC (10%)

Wet Granulation

FBD Drying Milling

Dry Blending Lubricant Disintegrant

Tabletting & Film Coating

Tablet Weight in-process & Film Weight Controls

Tabletting & Film Coating

CARBIDOPA LEVODOPA 50/200mg Extended Release Tablets

(Formulated with HPC/Carbowax modified hydroxypropylmethyl cellulose[1])

Carbidopa (18%)

Levodopa (66%) Color (trituration)

To Granulator Add Modified HPMC (8%)

Modified HPMC
HPC ~ 2-4%
Carbowax ~1%
HPMC [1] ~ 60%
HPMC [2] ~ 36%

99.9% Alcoholic Wet Granulation (12%)

High Shear Granulator control blending times and speeds

FBD Drying + Milling (0.8 mm)

Stearate blending time (5min)

Dry Blending Lubricant Glidant (0.5%)

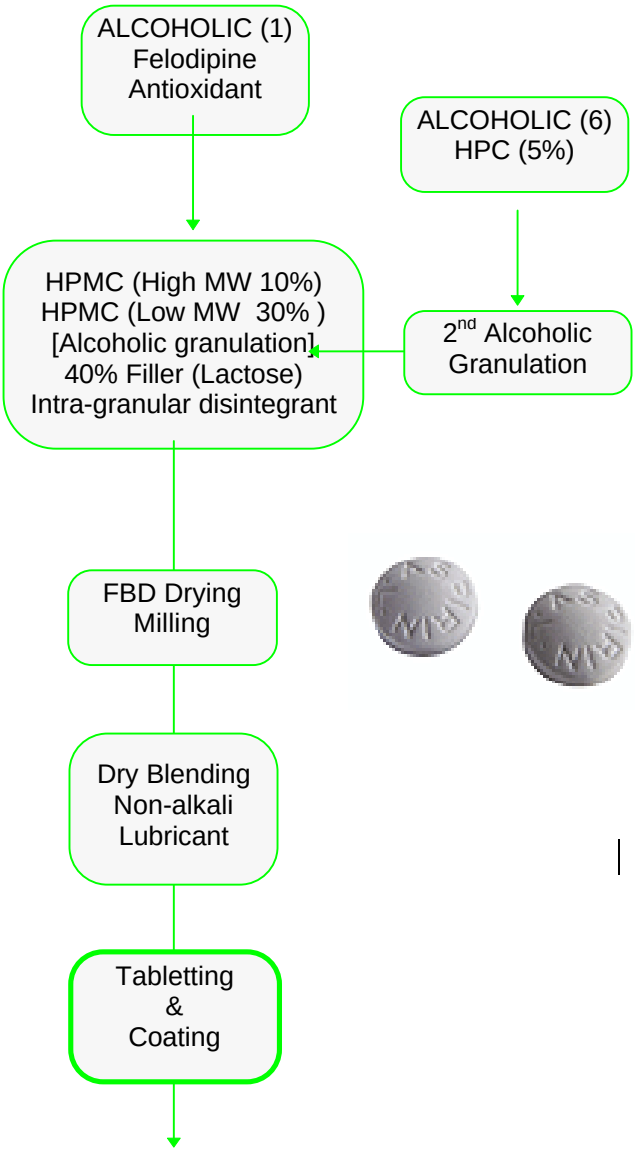
Non-Alkali Stearate (2-4%)

[1]With acknowledgments:- Handbook of Generic Development Controlled Release Tablets Volume 10 Edition 03 - Locum International Publishers Series ©2000.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

LOW LOADING DOSE - NON-AQUEOUS

FELODIPINE 2.5 mg ER Tablets (using alcoholic hydroxypropylcellulose (HPC))



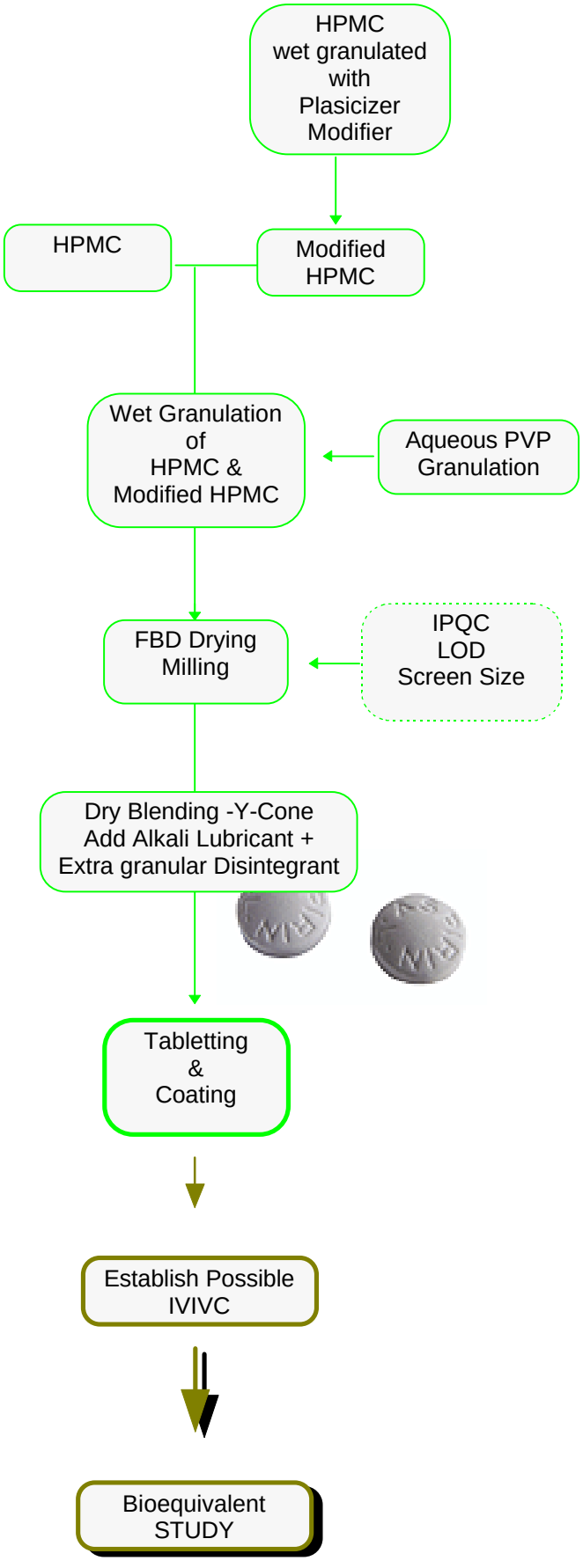
Dissolution curves produce a sustained release of 10 hours with the following dissolution profile

Felodipine 2.5 mg Dissolution Tolerances

Hours	Amount Dissolved %
1	1-10
2	10-30
6	42-68
10	NLT 75 (Individual)
10	NLT 80 (mean)
USP App. No 2, 50 rpm Paddle below stationary basket, Buffer pH6.8 1%SLS	

HIGH LOADING DOSE - Water Soluble

Erodible ER Tablets - (General Scheme)



ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

Table 4.1
Common Controlled, Modified, Delayed and Extended Release coating materials

Generic Name	Abb.	Soluble in	Properties
NON ENTERIC COATS			
Ethylcellulose	EC (DOW)	Ethanol, IPA organic solvents	Low Viscosity Aqueous films
Hydroxyethylcellulose (Union Carbide)	HEC	GI Fluids, Water	Low Viscosity Aqueous films giving clear solutions
Methylcellulose (Methocel™)	MC (DOW)	GI Fluids, Water, organic solvents	GI Fluids, Water insoluble Used as a film tougher
Methylhydroxyethylcellulose	MHEC (DOW)	GI Fluids	GI soluble film former
Hydroxypropylcellulose NF (Klucel LF™)	HPC (Hercules)	GI Fluids, Water, ethanol	Component in swelling or eroding polymers/matrixes
Hydroxypropylmethyl-cellulose NF (Methocel HG/ K-15 /E-5™)	HPMC (DOW)	GI Fluids, Water, ethanol, Methylene Cl	Component in swelling or eroding polymers/matrixes
Sodium carboxymethyl-cellulose	Na CMS (Hercules)	GI Fluids, Water, ethanol	Adjuvants as film formers / film modifiers
Polyethylene Glycols	PEG	GI Fluids, Water, organic solvents	Used as film modifiers / coat plasticisers
Carbopol 934 P (Union Carbide)	Carbo-waxes	GI Fluids, Water, organic solvents	Adjuvants as film modifiers / coat plasticisers
ENTERIC COATS			
Cellulose acetate (Kodac)	CAP	IPA, Acetone, ethyl acetate, alkalies	Dissolves in distal end of duodenum - add plasticisers
Hydroxypropylmethyl-cellulose phthalate (Shinetsu)	HPMCP	IPA, Acetone, alkalies pH > 4.5	Dissolves in proximal end of duodenum
Methacrylic acid co-polymer	Eugragit - L - S	pH > 6 pH > 7	Solubilized in alkali media Combinations used as Enteric coating plus sustained release
Polyvinyl acetate phthalate (Colorcon)	PVAP	IPA, Acetone, alkalies pH > 5	Dissolves in full length duodenum
Methacrylic acid esters			Combinations used as Enteric coating plus sustained release
Methacrylic acid polymers			Combinations used as Enteric coating plus sustained release
Shellac BPC 1963	MAP	GI Fluids, Water pH 7	Batch variability - irregular release - non reproducible.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

CHECKLIST

CL # P-HPGD-03-Y2K

Non active ingredients

'qualify the excipient performance at both ends of the given specification range'
'qualify the process performance with the chosen excipients'

1. Has the RLD's non actives been qualitatively identified ?	■*Yes* ■No
2. Are releasing and non-releasing controlling excipients identified?	■*Yes* ■No
3. Are the non actives referenced in the FDA's IIG book?	■*Yes* ■No
4. Has the maximum percentage not been exceeded for oral tablets?	■*Yes* ■No
5. Has the particle size and bulk density of key non actives (e.g. lubricants) been specified with an appropriate range?	■*Yes* ■No
6. Is the dissolution profile of the proposed generic formula similar to the RLD's profile?	■*Yes* ■No
7. Are the comparative 12 point dissolution values all within 5% of the RLD dissolution profile under normal and accelerated testing?	■*Yes* ■No
8. Is the granulation uniformity of content spread less than 4.0 - 5.0% with RSD , <6.0%?	■*Yes* ■No
9. Does the development protocol indicate that the final formula is manufactures at the lower and upper tabletting speeds ?	■*Yes* ■No
10. Does the firm regularly review the Pharmacopoeial Forum for proposed monographs and specifications for non-compendial excipients?	■*Yes* ■No
11. Has the firm reviewed all the suppliers for potential 'Approved Suppliers' as listed the Handbook of Pharmaceutical Excipients?	■*Yes* ■No
12. Is Purified Water USP used as an approved excipient granulating agent and coating suspension ingredient?	■*Yes* ■No
13. Have all the excipient specifications been reviewed in USP / NF, Ph. Eur / BP, and JP *and* the latest supplements and addenda?	■*Yes* ■No
14. For compendial excipients has the latest supplement been checked?	■*Yes* ■No
15. Does your generic firm have a current ' Approved Supplier SOP ' for non active ingredients?	■*Yes* ■No

Footnote : The words non active ingredient; inactive ingredient and excipient are all the same meaning and interchangeable in use.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

Non Release Controlling Excipients

'...Challenge the adjuvant systems during development and then optimize their formula concentration...'

Non Releasing Ingredients

Non release controlling ingredients are, antioxidants and chelating systems as well as lubricants and disintegrating excipients. They are not active ingredients nor are they neutral inactive ingredients, such as simple inert fillers but beneficial and essential non release controlling excipients, as they maintain the product quality and physical characteristics, as well as inhibiting impurity / degradant growth and enhancing processing ease and shelf life stability of the final product formula.

CHOOSING NON ACTIVE INGREDIENTS.

The evaluation of non release controlling excipients requires a thorough optimization and qualification protocol for:

- the anti-oxidant / chelating agent combination systems
- Solubility enhancing agent(s)
- Agents
- Lubricant(s)

Anti-oxidant and chelating agent combination systems

These systems maintain an active role by (a) minimizing the potency loss of the active ingredient(s) and (b) stabilizing the drug product's impurities during product aging.

The anti-oxidant system may well degrade significantly with time and therefore does not require any qualification or testing of its *upper* and *lower* operational limits.

Solubility additives may enhance both active & antioxidant

The addition of a solubility enhancing agent may enhance the dissolution parameters of a poorly soluble active ingredient and in parallel improve the anti-oxidant performance.

Typical solubility enhancers (Tween 80 or Polyoxyl 40 Hydrogenerated Caster Oil - Cremophore RH40™) may at times have a greater impact on the active drug dissolution profile and a probable reduction in tablet hardness, than enhancing the antioxidant activity of poorly soluble antioxidant agents.

It is important to establish and validate the impact of the antioxidant on drug assay and impurity profiles during the formula development (optimization) stage. Following this development path the actual antioxidant loss need not be routinely assayed during the product development stage or during commercial production.

Optimize the overall antioxidant system

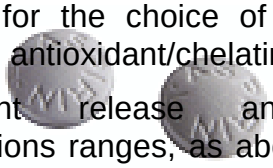
ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

Formula Optimization:

An anti-oxidant optimization protocol will enable drug developers to fully eliminate antioxidant release and check specifications from routine product release and stability testing requirements of the (pivotal) and subsequent commercial marketed batches of the specification type:

Release specification:	85.0 -105.0%.
Check specification:	55.0 -105.0%

Tablet formulations can and do consume the antioxidant system during the product's shelf life. Heavy metals may act as catalysts and degrade active and semi-actives. Thus the need to evaluate the chelating agent in combination with the antioxidant arises. Evaluating the total summed heavy metal content of the combined excipients (from their Certificate of Analyses) may provide a starting baseline for the choice of a suitable combined antioxidant/chelating agent.



Antioxidant release and check specifications ranges, as above have a very limited value in a drug development program. It may be appropriate to evaluate *once* the total quantity of antioxidant consumed during a three/six month accelerated stability evaluation.

The development formula optimization should tabulate the loss of assay potency and impurity / degradant growth for the active substance over an accelerated shelf life period of 0,1, 2, 3 (and 6) months at 40^0C / 75% RH

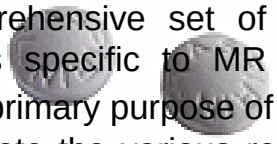
This formula optimization procedure simply *eliminates* any routine antioxidant testing in the future.

These antioxidant qualification studies are needed during the product development stage and once performed, close the requirement for any further testing. This is an important example of how careful product development can result in reduced QC routine finished product testing.

The first three commercial validation lots do not require *antioxidant* release / stability check testing as their formula inclusion was qualified during the development optimization phase.

Product release specifications must not become, in part, a substitute for incomplete development validation testing.

All pharmaceutical development units conducting drug research and development in to controlled release dosage forms should have a comprehensive set of development SOPs specific to MR formulations.

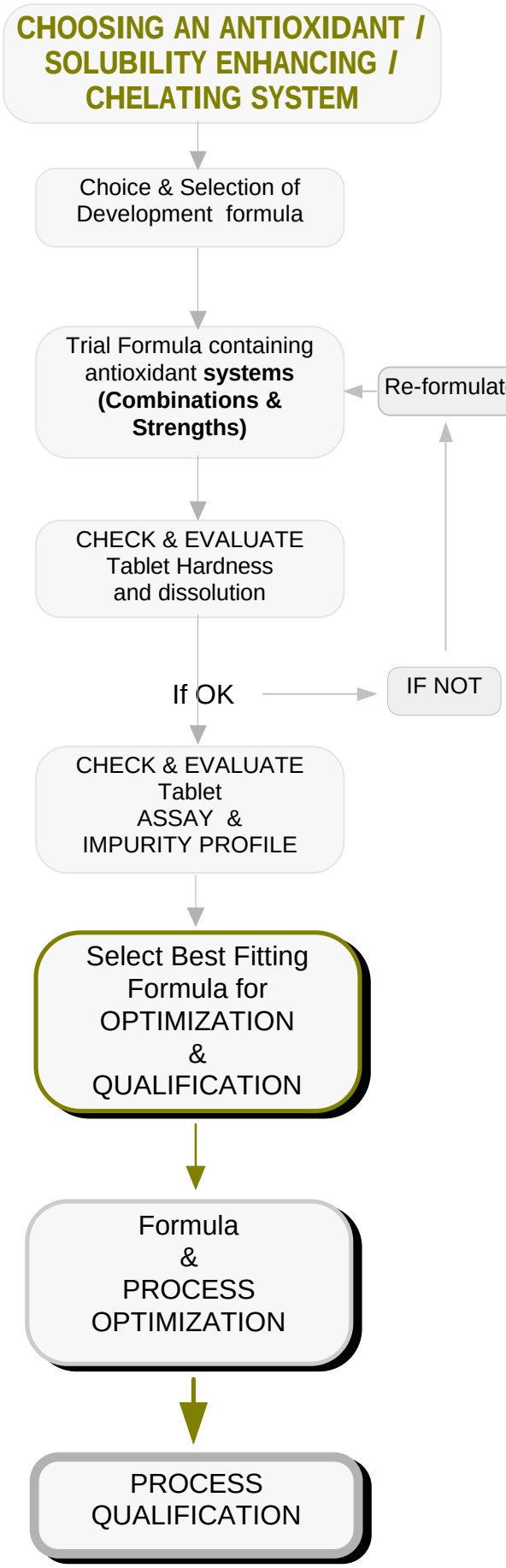


The primary purpose of the SOP is to translate the various regulations and guidelines, which are open to interpretation, into clear and concise sets of working instructions.

The following key development Standard Operating Procedures (SOPs) among others are recommended for a controlled release development unit.

IJGD-00-069Y - Choosing Non Actives Ingredients for Modified Release formula development.
IJGD-00-069Y Vendor Certification Requirements for Approved Non Release Controlling Excipients
IJGD-00-069Y Checking Excipient in the FDA *'Inactive Ingredient Guide.'*
IJGD-00-069Y Evaluation and classification of Release Controlling Excipients in MR / ER formulations.
IJGD-00-069Y Dissolution testing and evaluation of extended release solid oral dosage forms
IJGD-00-069Y Development, use and evaluation of Invitro Invivo Correlations in extended release solid oral dosage forms

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim



Release Controlling Excipients

An excipient in the final dosage form whose primary function is to modify the duration of the release of the active drug substance form the dosage form. Defined as a Critical Composition Variable.

Developers should provide appropriate justification (i.e. with supporting data of the mechanism of drug release and manufacturing process) for claiming any **Excipient** as a **Release Controlling Excipient** in the formulation of the modified release solid oral dosage form).

The functionality of the **Release Controlling Excipient** should be identified and stated as to the reason for its inclusion into the formula.

Non-Release Controlling Excipient: An excipient in the final dosage form whose primary function does not include modifying the duration of the release of the active drug substance form the dosage form. These non release controlling excipients (NRCE) are defined as a Non-Critical Composition Variables.

Note: the primary function of the excipient does not *significantly* affect the release of the active drug substance. (e.g. Magnesium stearate affects dissolution but not significantly.)

Developers should provide appropriate justification for claiming any **Excipient** as a **Non-Release Controlling Excipient** in the formulation of the modified release solid oral dosage form).

Consideration should be given as to whether the excipient is critical or non critical to the drug release.

The functionality of each **Non-Release Controlling Excipient** should be identified and stated.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

CHECKLIST

CL # HPGD-03-Y2K

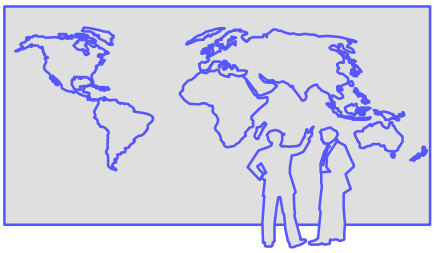
Validating the Semi Active Ingredients

' don't test a semi-active after it has been qualified...'

1. A full development validation/qualification study of the antioxidant has been performed during the development process?	■*Yes* ■No
2. Has a range of antioxidant percentages been qualified by development optimization studies. (e.g. lower [0.05%] middle [0.10%] and upper [0.15%])?	■*Yes* ■No
3. Does the antioxidant percentage selected represent the lowest % value to minimize impurities and degradants during the inferred product shelf life?	■*Yes* ■No
4. Has the overall excipient formula been evaluated for total heavy metal content from the inactive C of A's and product specification data sheets?	■*Yes* ■No
5. Have reducing agents, antioxidant synergist and sequestering agents that have not been appropriately validated, been excluded from the product formula?	■*Yes* ■No
6. Does the active ingredient remain in the check specification range (90.0 - 110.0 of labeled amount) at the end of accelerated stability testing?	■*Yes* ■No
7. Does the potency of the active ingredient decrease when the chelating agent is removed from the product formulation during normal and aging studies?	■*Yes* ■No
8. Have range studies been performed to evaluate the optimum amount?	■*Yes* ■No
9. Has the product formula been evaluated at lower, middle and upper antioxidant percentages and evaluated against active assay values?	■*Yes* ■No
10. Has it been clearly established that the inclusion of chelating or an antioxidant synergist positively enhances the action of the antioxidant?	■*Yes* ■No
11. Has potency loss of the semi actives been fully demonstrated during the product development stages to establish valid specification ranges?	■*Yes* ■No
12. Does the stability testing protocol *only* evaluate formula specifications that are directly impacted by the aging process ?	■*Yes* ■No
13. Has a complete product development profile of the antioxidant been evaluated in order to eliminate routine release and stability testing of the antioxidant agent during commercial manufacture ?	■*Yes* ■No
14. Is the stability testing protocol for the pivotal batch a logical development sequence from the product development work ?	■*Yes* ■No

Footnote :
Bold numbers in checklist indicate this work must be qualified and or validated before manufacturing the Process Qualification Batch, which actually marks the end of the product development stage.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

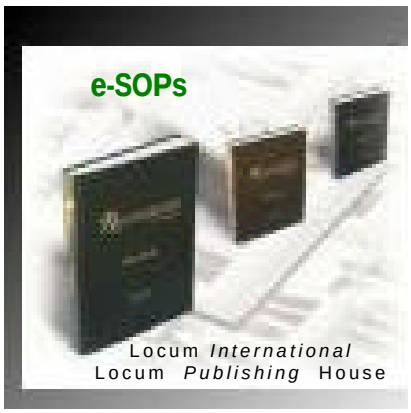


Series ISSN 0793 7407
A *Series* Publication in association with
The International Association of Generic & Innovative Drug Manufacturers.

Essential Pharmaceutical Generic Drug Development

e-SOPs

- **Pharmaceutical**
- **Analytical**
- **Decision Trees**
- **Bioequivalency**
- **Microbiological**
- **Quality Control**
- **Scale Up**
- **Cleaning Protocols**
- **All Validations**
- **Regulatory**
- **Pre Approvals-PAIs**
- **Annual Reports**



Electronic Standard Operating Procedures.
Available on 3.5" 2MB electronic disks for immediate in-house use. Guidelines provided on how to convert development SOPs into your own customized research-based-development system that meet all international regulatory guides, guidelines and regulatory requirements. **e-SOPs**™ can be edited to meet your development units own in-house needs. Designed for Generic and NDA use.

CD ROM development and process SOPs provide complete Development, Formulation, Scale-up, Process Qualification; pivotal and final validation batches; analytical, cleaning and process validation; essential documentation and OGD regulatory know-how that is essential for a successful product development and a speedy FDA approval, saving queue-time and development dollars.

Essential information for Development Pharmacists, R&D Chemists, QA and Regulatory personnel. Allows management to understand the nuts and bolts on Generic ANDA and EC DEVELOPMENT and filing in the most cost effective way.

CD ROM available at: **$299.**

In association with the
International Association of Generic Drug Manufacturers. -
Contact info@locum.co.il
Fax: + 972-9 7494 532 / 965

A Locum House Publication

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

CONTROLLED RELEASE OVERVIEW

Developing CR Formula

'...plan the development stages into a CR Development SOP - then carefully work the strategy of what you planned to do'...

CR DEVELOPMENT

Developing controlled release (CR) dosage forms differ in two significant aspects when comparing to the development of immediate release (IR) formulations. Firstly they consists of two distinct types of ingredients other than the active. These ingredients are:

- Release Controlling Excipients
- Non-release Controlling Excipients

Both types of controlling excipients need to be well chosen, optimized through a series of trial formulations and finally qualified - both qualitatively and quantitatively.

Rule One

Qualify the Controlling Excipients Release and Non-release

The second key development stage is to achieve matching dissolution profiles between the developing formula and the reference drug and then establish an in-vitro in-vivo correlation of the controlled release preparation to the reference product. The preferred way to establish an IVIVC is to undertake a single dose *cross-over* pilot biostudy when the formula has been fully fleshed out to the final formula development status.

Problems with developing CR formulas are that 12 point comparative dissolution profiles (CDPs) can be formulated to match the innovator's profile or nearly superimposed upon it, however this converging correlation does not necessary imply instant bioequivalence. Adjustment are usually made to the pilot study formulation or dissolution parameters in order to establish an initial Level C IVIVC using a single point correlation around the $C_{max.}$ (obtained from the single dose cross-over biostudy plasma levels.)

Rule Two

Match the Dissolution Profiles in Multimedia

A Level C IVIV correlation obtained from a pilot biostudy can be useful in the 'pilot formulation development' of the controlled release preparation. CR developers usually produce three very similar formulated preparations (with 'slow', 'medium' and 'fast' dissolution profiles, ~10 - 15% apart) and then evaluate an appropriate correlation. Keeping the number of pilot biostudies to a minimum is an essential cost effective tool. One pilot study (3-6 volunteers) prior to the IVIVC and full scale bioequivalence study is all that is generally needed.

Rule Three

Do a Single Dose PRE-IVIVC Biostudy

Two matching processes are evolved. Initially harmonizing the test and reference CDP to coincide. Secondly adjusting the dissolution profile in the

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

media of choice, and other dissolution media, pH and agitation parameters designed to highlight and discriminate test & reference drug differences.

The first is to develop an equivalent formula and the second to obtain a possible Level A correlation.

Rule Four

Establish a Level A IVIV Correlation

Study Subjects:

Bioavailability studies for IVIVC development normally contain sufficient subjects (healthy volunteers) to adequately characterize the performance of the controlled release drug product. Various scenarios exist.

In IVIVC Studies Subjects May Range from 6 - 36

A well formulated CR preparation supported with extensive comparative dissolution profiles can reduce the number of subjects (& cost) required.

A initial pilot study requiring a Level C: needs 3 - 6 subjects (Initial mini-single dose studies with 1-3 subjects have been used to obtain AUC, $C_{max.}$ $T_{max.}$ and an indication of the overall shape of the plasma concentration curve for ongoing formulation development).

Advanced studies requiring full IVIVC subject data sets have ranged from 6 to 36. New drug formulations (NDAs) tend to have greater subject numbers (up to 36) than ANDAs (as low as 6).

Do's and Don'ts.

Do check the active solubility at different pH values (pH1.2 ; 4.5 ; 6.8)

Do check the drug product's dissolution profile in different pH media (pH1.2 ; 4.5 ; 6.8)

Do check the dissolution profile at different rpm speeds using both the basket & paddle (100;150 / 50;75 rpm). Generally the lower the solubility of the active material in the matrix the higher the rpm speed may be required.

Do develop invitro dissolution methods that DO discriminate between various formulations and process procedures.

Do fix this discriminating dissolution procedure well before any single dose pilot study or full IVIVC is undertaken.

Do optimize the discriminating dissolution procedure to get the best 1:1 correlation *once* the invivo parameters are known.

Do incorporate time scaling as long as the time scale factor is the same for all formulations tested.

Don't compare different formulations on different time scales.

Don't use a Level B Correlation for regulatory purposes as these do not discriminate between different formulations that display similar mean resident plasma time curves.

ADEQUATE DATA

An important concept in CR IVIV development is that the less data available the poorer the predictive ability. Thus more data will be needed to predict a complete IVIV correlation. Enhancing this data quality by evaluating different formulations (~3) with up to 10% differences (percent dissolved) in invitro dissolution profiles would produce different invivo release rates and thus differing plasma concentration levels.

INDEPENDENT DISSOLUTION

If invitro dissolution is shown to be independent of the dissolution conditions (e.g. pH and agitation) and if the invitro dissolution profile is shown to be equal to the invivo absorption or dissolution profile, then the results for a single formulation (one release rate) are generally quite sufficient data.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

THE CR DEVELOPMENT SOP

The development SOP for controlled release dosage forms is a vital document that contains each stage of the development process of the new generic drug up to and including the pivotal batch (submission batch).
This document brings all the interacting departments, i.e. pharmaceutical, analytical (assay and dissolution) and stability units together to form one development program.

CREATE IVIVC checklists and development criteria

The overall development procedure requires that the product formula, manufacturing process, controls and final product specifications (including stability) are formulated, optimized and qualified through a *series* of lower and upper limit formula and process specification qualifications during the *overall* product development phases.

These composite validation qualifications are demonstrated again for regulatory purposes in a finalized, single, continuous process during the manufacture of the pivotal batch and further demonstrated in the three validation (commercial) batches.

The validation process shows that all the ranges and limits in a manufactured batch, produce the desired drug product according to the written specifications.

Optimization and qualification of specification limits and process parameters are developed *before* the pivotal batch manufacture, in specific development batches, namely the process optimization (PO) and qualification batch (PQ). The PQ batch is in fact the real end point of the product development phase.

THE DEVELOPMENT REPORT

The development report documents all the results of the development process as highlighted from pre-formulation to the pivotal batch filing of the ANDA The development notebooks and interim reports provide the basic data & results to this development report.
The development report is completed after the pivotal batch has been packed, tested and placed on accelerated stability. All product specifications, procedures and qualifications are completed prior to starting the pivotal batch manufacture. Major development stops at the conclusion of this batch.

This batch is the ANDA demonstration batch for filing with the FDA that demonstrates a well developed, rugged product formula and process.

AN EFFECTIVE IVIVC Eliminates Post Approval Biostudies

Scale-Up and Post Approval Changes (SUPAC-**MR**) are permissible after the pivotal batch but MUST follow the SUPAC-MR rules for each change made. Where an IVIVC exists additional biostudies for post approval changes are *seldom* warranted

The three validation batches, - sold as commercial products, demonstrate that the formula and process consistently give the same product specifications and are comparable to the bioequivalent batch (i.e. pivotal).

The development process simply establishes the ruggedness or robustness of the formula, manufacturing process, product specifications and the type of equipment used. The pivotal and validation batches initially demonstrate and then later prove the consistency of the overall drug product and process.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

CHECKLIST

CL # HPGD-03-Y2K

DEVELOPING CR FORMULA

'...combine the development stages into an overall 'Development Report' - what did you really do?...'

1. Is a 'Development SOP' for the **CR / MR** dosage form available?	❑***Yes*** ❑No
2. Does a SOP specifying the contents of the Development Report?	❑***Yes*** ❑No
3. Is the active ingredient characterized for particle size and bulk density (crystal structure / polymorphism) for each approved supplier?	❑***Yes*** ❑No
4. Are the source and supply of the excipients characterized?	❑***Yes*** ❑No
5. Is the source and supply of the container/closure characterized (1998 Guideline)	❑***Yes*** ❑No
6. Does the SOP indicate that non-compendial active material assays requires a validation and stability indicating assay?	❑***Yes*** ❑No
7. Does the SOP required full analysis of the reference listed drug (RLD), its impurity profile and stability characteristics?	❑***Yes*** ❑No
8. Is an historical listing and summary of all experimental batches manufactured required by a SOP?	❑***Yes*** ❑No
9. Is a multipoint dissolution profile of the product formula at key stages required and compared to the RLD? Are IVIVC investigated (Sept.1997 Guideline[1])	❑***Yes*** ❑No
10. Do the critical manufacturing procedures, critical process parameters and key in-process controls require optimization and verification studies ?	❑***Yes*** ❑No
11. Is a process of tightening / qualifying the product specifications, (based on batch analysis) evident as the development process undergoes optimization?	❑***Yes*** ❑No
12. Does the development process identify the critical processing steps for the validation protocol with the potential to affect the product?	❑***Yes*** ❑No
13. Hardness and dissolution tests qualified (Tablet Hardness Qualification)?	❑***Yes*** ❑No
14. Does the analytical development require a <u>final</u> validated assay and stability indicating (SI) assay well <u>before</u> running the pivotal batch?	❑***Yes*** ❑No
15. Are stability study assays of the PO and PQ batch required to be tested by the validated assay procedure and SI analysis?	❑***Yes*** ❑No

[1]Development Evaluation and Application of In Vitro/In Vivo Correlations (September 1997 BP2)

Footnote : Bold numbers in checklist indicate that this work must be checked and approved before **formulation** work starts.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

CR Formula Development

'...research and evaluate the reference listed drug thoroughly...'

ANDA Preparations

The development of a oral dose **CR** tablet requires seven key decisions points:-

- reference listed drug (RLD)
- active material (source/supply)
- non-active ingredients (source/supply)
- container-closure system (as RLD)
- Invitro Invivo Correlation data
- Comparative dissolution procedure
- Bioequivalence to the (RLD)

The RLD is chosen from the FDA 'Orange Guide' (now on the Internet).
('Approved Drug Products with Therapeutic Equivalence Evaluations' - current 18th Edition 1998).

Active substance

The active drug substance is chosen according to standard criteria. Correct choice is both critical and time consuming. Key parameters include:-

- Analytical profile - similar to RLD under normal *and* stress conditions.
- Impurity profile - similar to RLD under normal *and* stress conditions.
- Approved supplier must meet all ANDA regulatory documentation requirements.
- Active Material specifications remain constant - batch-to-batch (**not** R&D or non-commercial batch)
- Able to supply for the next 8-10 years at the similar specifications after ANDA (pivotal) batch manufactured.

Using the RLD's Active Material

Ideally the same supplier of the active drug substance as used by the RLD, is the most cost-effective in the long term, as IVIVC, stability, impurity, and aging profiles are similar.

In-active ingredients (excipients)

The product formula of the generic **CR oral tablet** does not have to contain the same inactive ingredients at the same quantities as the RLD, as do sterile or semi-solids dosage forms. The qualitative ingredients are required to be in the OGD *Inactive Ingredient Guide (IIG).*

The FDA publish the *Inactive Ingredient Guide.* Inactive ingredients found in approved drug products in the US are listed in the IIG.

The amount of the non-release controlling excipients and release controlling excipients in the product formula should not be greater than the highest concentration previously found in an approved product for the same route of administration (i.e. oral route)

Development SOP's are clarifying the choice of inactive ingredients for pre-formulation and formulation development are an effective tool.

The choice of a well known excipient manufactures with an established excipient range is very important as long term stability, dissolution and aging problems are minimized or avoided. Thus source and supply of inactive ingredients for oral CR tablets are paramount.

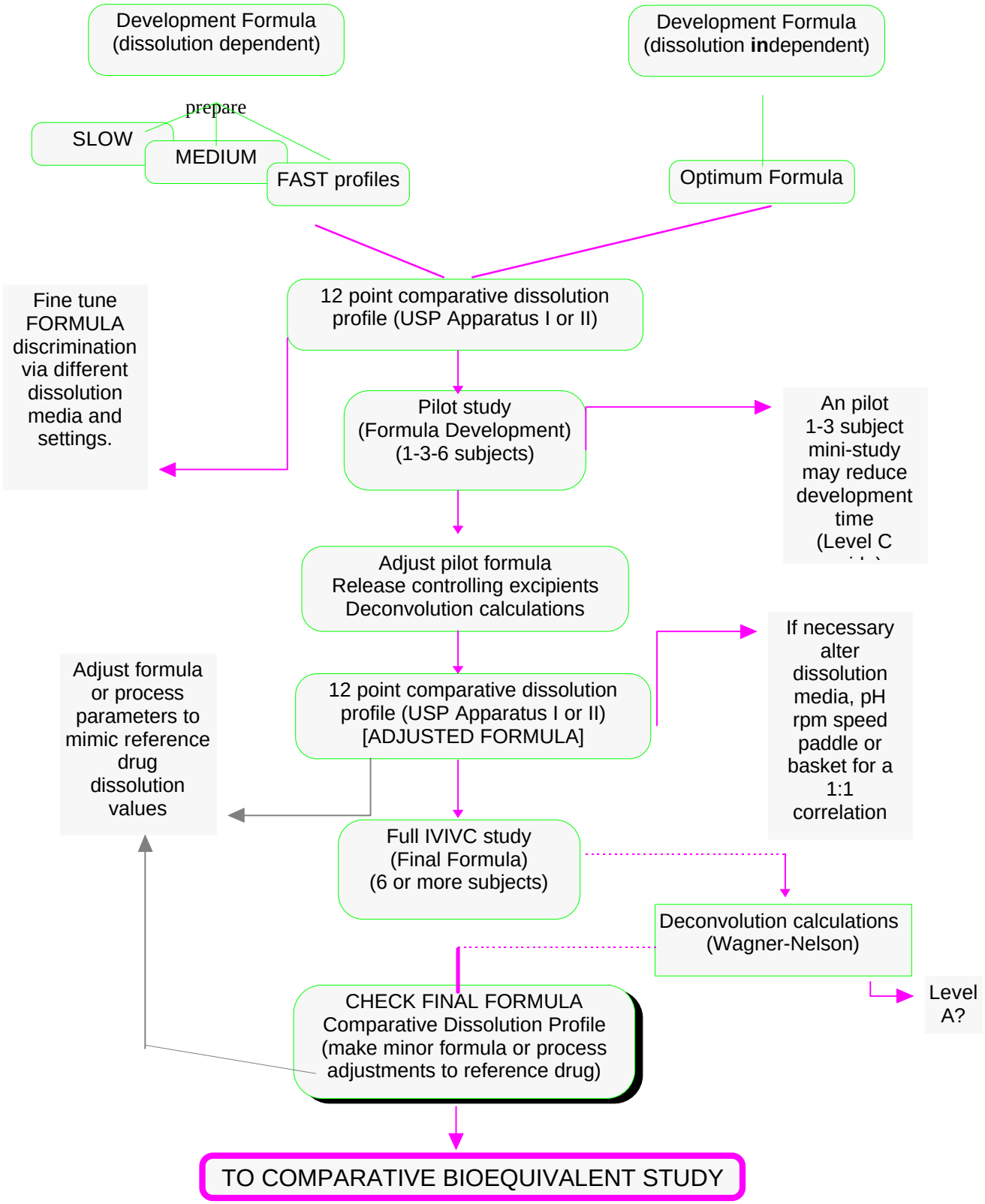
Container closure systems

The drug product container-closure system should be a similar material composition as the RLD container-closure system.

The degree of product protection by the container-liner-closure system must prevent physical, chemical and microbiological changes on storage and during customer-consumer use.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

USING A TYPICAL IVIV MODEL



ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

CHOOSING & USING THE LEVELS

LEVEL A - ['Concentration Profile']

A MULTI point-to-point evaluation between an invitro dissolution profile and an invivo dissolution profile

A mathematical model that predicts the relationship between invitro and invivo curves. The dissolution profile and the plasma drug concentration profile evaluated mathematically

The most useful and informative level

Normally a linear relationship is developed. Scaling factors permissible

LEVEL B - ['Time Profile']

NOT a point-to-point correlation

A mathematical model that predicts relationships between invitro and invivo time courses. Compares the mean invitro dissolution time and mean invitro dissolution time (or rate constant)

The least useful informative level

Uses Statistical moment analysis. CANNOT discriminate between different invivo curves with the same mean residence time

LEVEL C - ['Single Point']

A SINGLE point-to point evaluation between an *invitro* dissolution <u>value</u> and an *invivo* dissolution <u>value</u>

Establishes a single point relationship between a single dissolution parameter (say a 4 hr assay) and a single invivo parameter (i.e. AUC , or T_{max}, or C_{max})

The most useful SINGLE point level

Use for pilot and development or optimization formula/process studies

DOES not show the shape of the plasma concentration time curve (CRITICAL!)

MULTIPLE LEVEL C - ['Some Points']

A One or Two point evaluation between invitro dissolution <u>values</u> and invivo dissolution <u>values</u>

Establishes a partial relationship between dissolution parameter (2 & 4 hr assay) and <u>some</u> invivo parameters (AUC , T_{max} , C_{max})

Useful to extend to a Level A correlation

DOES not show the <u>whole</u> shape of the plasma concentration time curve (Try Level A)

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

➢CHECKLIST➢

CL # HPGD-04-Y2K

CR FORMULA DEVELOPMENT

'...Systematically compare your developing product to the chosen RLD at all key stages...'

1. Has the Reference Listed Drug (RLD) been chosen from the Orange Guide?	■***Yes*** ■No
2. Has the RLD been purchased in all the proposed marketing sizes ?	■***Yes*** ■No
3. Have different batch numbers (3 lot #'s) of the RLD been purchased?	■***Yes*** ■No
4. Confirm if the RLD is of recent manufacture (analyze new samples)?	■***Yes*** ■No
5. Conform that at least 10-20 samples of each RLD lot # and pack size are available for physical, chemical (assay and impurities), dissolution and stability testing?	■***Yes*** ■No
6. Confirm if the RLD has been placed on stability at 40° C for 3 months for evaluating potential degradation and impurity levels?	■***Yes*** ■No
7. Confirm if the impurity profile of the RLD has been evaluated?	■***Yes*** ■No
8. Has reverse engineering of the RLD formula been performed?	■***Yes*** ■No
9. Have the release and non release controlling excipients (maximum amounts) been crossed checked in the IIG? (especially for unique or unusual release controlling excipients)?	■***Yes*** ■No
10. Are the release and non release controlling excipients compatible for oral dosage form use (composition and strength)?	■***Yes*** ■No
11 Have the RLD formula been reviewed in the International Drug Compendia (Italian, French, Swiss) for formula composition data?	■***Yes*** ■No
12. Has the FOI system been used to gather data on the Innovative drug (e.g. Summary Basis of Application)?	■***Yes*** ■No
13. Has a full analytical profile range been determined from analysis of the various batch lots of the RLD (at least 3 lots #'s for Assay; Content Uniformity; Impurities and Dissolution Profile range)?	■***Yes*** ■No
14. Has the chosen RLD undergone stress testing to establish the level of its degradation products?	■***Yes*** ■No
15. Has a multipoint dissolution of the several RLD batch lots been evaluated to assess the consistency of the RLD's dissolution parameters?	■***Yes*** ■No

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

➢CHECKLIST➢

CL # HPGD-04-Y2K

DEVELOPING CR FORMULA

'...combine the development stages into an overall 'Development Report' - what did you really do?...'

16. Confirm that the analytical dissolution method (UV/HPLC) has been validated before comparative dissolution profiles (CDP) are performed?	■***Yes***■No
17. Reject early CDPs using non-validated dissolution assays?	■***Yes***■No
18. USP apparatus I (basket/100rpm) or II (paddle/50-75rpm) is the preferred dissolution method? Note: basket speeds generally higher than paddle speeds.	■***Yes***■No
19. USP apparatus III (reciprocating cylinder) or IV (flow through cell) may be utilized for *some* ER formulation?	■***Yes***■No
20. Water or buffered solutions (**NMT** pH 6.8) are appropriate dissolution media?	■***Yes***■No
21. Poorly soluble drugs may have an solubility enhancer added to the dissolution media (1% sodium lauryl sulfate)?	■***Yes***■No
22. Non aqueous and hydroalcoholic (ethanol or IPA) are not/rarely recommended or appropriate dissolution media for IVIVC?	■***Yes***■No
23. A 12 point dissolution profile is normally always required?	■***Yes***■No
24. Dissolution profile RSDs or coefficients of variation (CVs) should be well under 10%. Target value around 4 - 6% RSD?	■***Yes***■No
25. Four to Six sampling time points should be selected to define an adequate dissolution profile range e.g. (0, 4, 8, 12, 16, 20hr. / or / 0, 2, 4, 6, 8 hr.) ?	■***Yes***■No
26. Twelve (12) individual dosage units per batch/lot and six (6) sampling points is the ideal dissolution profile set-up?	■***Yes***■No
27. Examine the RSD per sampling point to evaluate formula/process homogeneity.	■***Yes***■No
28. Develop the IVIVC in the fasted state, study (cross-over human subject study)?	■***Yes***■No
29. Initial pilot studies for end-formula development (final release controlling excipient optimization) require only 1-3 subjects? - alternatively use…	■***Yes***■No
30. Confirmation IVIVC at final formula stage, requires 6 or more subjects?	■***Yes***■No
31. Use Level C for an initial formula development guide - 3-6 subjects?	■***Yes***■No
32. Use Level A for *final* formula confirmation studies with 6 or more subjects?	■***Yes***■No

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

STANDARD OPERATING PROCEDURES

SOP # HPGD-02-Y2K

CR FORMULA DEVELOPMENT

The following selected model Standard Operating Procedures are recommended for a generic development unit:

DEVELOPMENT SOP

HPGD-02-Y2K Setting up a General Development SOP.
HPGD-02-Y2K Setting up a *Product Specific* Development SOP.
HPGD-02-Y2K Contents of a Development SOP - Oral **CR** Tablets.

DEVELOPMENT FORMULA

HPGD-02-Y2K Vendor Certification Requirements for Product Development.
HPGD-02-Y2K Formulation of **CR / ER**[1] ANDA Oral Tablet Preparations
HPGD-02-Y2K Establishing an IVIVC in **E**xtended **R**elease *Oral Dosage Forms).*
HPGD-02-Y2K Standard Procedures for Generic **CR** Product Development

DEVELOPMENT REPORT

HPGD-02-Y2K SOP for Development Reports.
HPGD-02-Y2K Contents of a Development Report - Oral **CR** Tablets.
HPGD-02-Y2K Parameters for Process Optimization and Process Qualification.

NOTE ON DEVELOPMENT

The intent and purpose of the pivotal batch is as a final demonstration that the formula, process and controls are well developed and tested during development stages and really need no significant changes or further process qualification. However scale-up changes *can* take place *within* the SUPAC **MR** rules after manufacturing the pivotal batch. These SUPAC **MR** rules govern the **S**cale-**U**p from pivotal (10% or more) to commercial (100%) and **P**ost-**A**pproval **C**hanges i.e. changes after registration approval has been given.

ER[1] Extended Release Dosage Form: A dosage form that allows a *reduction* in dosage frequency as compared to that presented by conventional dosage forms such as a solution or an immediate release dosage form

[End of Document]

Edition No. : 01	Effective Date:	APPROVED:
Ed. Status New	DD/MM/2000	_____ _____ _____ _____/_____ Department RD RA QC / Q A

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

From Pre-formulation to **End** Formula

'Research and evaluate the CR formula thoroughly'

Overview of Product Development Stages for a Modified Release Drug Product

Literature search:

Preliminary activities in a drug development project start with a comprehensive review of authoritative reference books on the pharmaceutical and analytical parameters and attributes of the chosen drug. Reference works such as the US Pharmacopoeia, (and supplements) B.P., (and addenda) Ph. Eur.; Pharmacopoeial Forum, Physician's Desk Reference; Martindale; Merck; Florey; and Vidal are thoroughly reviewed on physical and chemicals aspects of the active ingredient and potential formulations. An extensive computerized online search relating to the specific drug substance and the drug product is conducted.

The USP Supplements and BP Addenda are carefully screened for new monographs at regular intervals during the ongoing drug development program as a new active monograph may be published during the actual product development stages.

Finally the Innovator's *Summary Basis of Approval* is obtained via the Freedom of Information Services for data review.

Patent Evaluation:

The Innovator's overall patent situation is thoroughly evaluated with special reference to *product* and *use* patents. Exclusivity and Patent data is reviewed in the FDA's Orange Book *"Approved Drug Products with Therapeutic Equivalence Evaluations"* Edition 20 (2000)

Under the section titled 'Prescription and OTC Drug Products - Patent and Exclusivity Data', the patent number and patent and exclusivity expiration dates are obtained. The latest cumulative index to the Orange Book may be viewed on the FDA home page.

Use patents (i.e. therapeutic uses) are indicated with the symbol "U" followed by a number representing a specific therapeutic use. A corresponding list of therapeutic uses are given.

Exclusivity information for a specific category is indicated by an abbreviation followed by the date on which the exclusivity actually expires (NCE - Dec 30, 2000) NCE = New Chemical Entity.

Sourcing of Raw Material:

Sourcing for a potential suppliers of the active material.

At least two approved suppliers of active material should be qualified. Request samples from potential suppliers. Exercised care that the active material samples received always represent a production batch and are not from an experimental batch lot where the specifications, physical (bulk density and particle size) and chemical (impurity profile), may change with time.

Once a suitable active supplier has been located sufficient material should be ordered to allow for preliminary pre-formulation development to begin prior the full analytical testing of the suppliers sample.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

This is a time saving device as a full analytical profile (with BET, polymorphism evaluation etc.) may take one or two months to fully appraise.

Testing of Active Material Sample:

Initiate chemical evaluation with the analytical development laboratory as per official pharmacopoeia monograph (Pharmacopoeial Forum method, if present at time), or alternatively by the supplier's test method or a modified in-house analytical method based on the supplier's method and specifications, where no official monograph exists.

Marketing input requirements:

Based on the Innovator's product obtained from the market place the following product presentation information is acquired;

- ◊ tablet shape, (possible patent on a special tablet or caplet shape.)
- ◊ tablet color - individual color for each dosage strength
- ◊ proposed code / symbol or lettering for punch embossing
- ◊ proposed packaging sizes (smallest; intermediate; and largest pack sizes)
- ◊ Container - closure types. (glass, plastic securitainer, blister pack.)

Innovator's Tablet Testing:

Physical Testing

Physical tests evaluating the innovator's product for tablet color, weight, thickness, hardness range, friability, etc. as well as an evaluation of the tablet punch diameter (round) and shape (caplet) are now undertaken.

Inactive Ingredient Identification

Evaluation of excipients used in innovator's product are obtained partly from the package insert, and / or the PDR with supporting analytical and microscopic tests confirming, where possible, the identification of the excipients morphological characteristics and crystal shapes.

Limited **i**nformation on the presence of specific excipients can be obtained from microscopic observation. For example, the pharmacognosy of Avicel™ and different starches have very specific shapes and are thus easily identified.

Dissolution Profile

Perform a 12 tablet dissolution profile using USP monograph / FDA method or in-house method (which ever is available at the time of testing).

First batch of Active Material:

Active Material Release

This initial active material lot is released by the Development (or plant QC laboratory if the material is intended for pivotal batches), according to pharmacopoeia, (or in-house methods and specifications in the absence of a pharmacopoeia monograph). Release of material without full monograph testing is allowable if the material is not intended for a Process Qualification (PQ) and pivotal batch.

Physical Characterization of Active:

A full analytical evaluation of the approved supplier active material is now undertaken that will finally end in a comprehensive Analytical Development Report.

Standard physical parameters for evaluation are:

- Polymorphism (TGA / DTA)
- Polymorphism (DSC - Calometery)
- B.E.T. surface analysis
- IR Solid State / X-Ray Diffraction (XRD)
- Particle size distribution
- Particle size distribution method
- Bulk density
- Microscopic morphology
- Crystal habit
- Solubility (different pH levels,25^{o}C)

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

Physico-Chemical:

- Optical rotation
- Enantiomeric purity
- O.V.I. testing (organic volatiles)
- Impurity profile

Evaluation of raw material supplier:

- DMF availability
- Compliance with USP monograph
- Impurity profile and stability profile
- Commitment to maintain written physical / chemical specifications
- Statement of non-patent infringement

Interim analytical and pre-formulation development report:

The findings of the initial development work are summarized and tabulated into an interim development report, covering the analytical and pre-formulation findings that will eventually form part of the overall comprehensive product development report.

DEVELOPMENT LOTS

Developing the formula through a series of mini experimental trials involves evaluating the type of granulation process and the physical properties of the granules / tablets formed. Steps for the choice of a suitable process are:

- ♦ Evaluation of suitable excipients:
- ♦ Excipient compatibility using DSC method and 55° C stability.
- ♦ Dry mixing, slugging, milling (dry granulation procedures)
- ♦ Wet granulation (by low / high shear mixer or F/Bed sprayer), etc.
- ♦ Determination of granule moisture content (~1-3%) and temperature setting for testing LOD. (Mettler™,/ Computrac™ Infra Red Dryers etc.)

⇒ Physical properties of granulate:

- Flow
- density
- compressibility.

⇒ Physical properties of tablets:

- ♦ Weight
- ♦ hardness
- ♦ thickness (core & coat)
- ♦ friability, dissolution etc.

Choice of Punch and Die Set:

Ordering of punches

The Pivotal Batch as well as the Process Qualification batch should be compressed on a production (or production type) machine, e.g. Manesty™ Fetta P1200™; Kilian RTS™

Production supervisors are consulted regarding the choice of the compression machine. Avoid any manufacture with worn-out punch and die sets. The Punch Supervisor initiates the ordering of the embossed or scored punch and die sets suitable for the proposed *marketed* product. Scoring is important. Tablet shape and scoring can affect the dissolution parameters. Maintaining the proposed marketing tablet shape is an important factor at the dissolution profile evaluation stage.

Analytical testing of tablets / caplets:

Dissolution in USP medium and other relevant media versus innovator's product as well as the Uniformity of Content for low drug active concentrations are two critical development parameters. Refer to the USP requirements for Uniformity of Content vs. uniformity of dosage units, where the active content is above or below 50 mg.

Active Stability:

Ordering of raw material for Process Qualification (PQ) and Pivotal Batches.

On accepting the stability profile data from the active material evaluation, coupled with the results the from the development lots, the active supplier is now approved. Order sufficient material for the PQ and Pivotal Lot manufacture.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

It is important to use same batch of active material for the PQ and Pivotal batch, as these two batches are somewhat complementary to each other and form the culmination of the formula and process development.

An average of 2-3 months may be required from date of order to receipt of approved active material, during this period process optimization batch(es) and scale-up work is performed.

PROCESS OPTIMIZATION

Process optimization is the process of fine tuning the manufacturing process and making minor adjustments to the formula or process. It should be performed on a larger batch size so that the potential problems of scale-up can be addressed, as they arise with larger size manufacturing equipment that use the same operating principle. Fine tune the effects of granulation and compression parameters may include;

- granulation speeds (i.e. blade speeds (i.e. chopper 1 and II in high speed Granulators -e.g. Diosna™)
- number of mixing stages (one or two for high shear mixing)
- mixing times and overall mixing
- solvent amounts and rate of addition
- screen size of granulate (e.g. 0.6-0.8 mm) with respect to tablet properties.
- Drying temperature versus LOD obtained and its effect on granulate and tablet properties (capping, flow, sticking, and hardness).
- Blending times (short) - the effect on uniformity, lubricity and dissolution.
- Effect of hardness on tablet properties (aging, dissolution, friability, hardness limits).
- Qualify the Hardness Range Limits
- Final evaluation of stability profile.

Process Optimization Report:

The findings of the process optimization work are summarized in an interim process report, outlining the optimization data for final presentation in the product development report.

PROCESS QUALIFICATION

(The PQ Batch)

The process qualification batch is manufactured in order to detect any problems that may arise during the manufacture of production size batches, permitting a timely solution before the manufacture of a pivotal batch.

The process qualification team and production personnel should discuss formula and process instructions and decide on optimum batch size, and then define critical processing steps and test parameters to be evaluated.

Master Documentation:

The project researcher finalizes the Batch Formula and Manufacturing Instructions documentation package for signing by the authorizing personnel.

The process qualification team prepares the PQ Protocol and consults with the analytical coordinator with respect to the analytical testing requirements of the many PQ samples.

Production personnel are present during the process qualification batch run, as this process usually mimics production conditions and acts as a precursor to the upcoming pivotal batch. The suitability of the process documentation package is evaluated during this run. Amendments are added where necessary to effect *practical* documentation for the pivotal batch.

Upon completion of the process qualification batch testing, a Process Qualification Report is formulated.

ANALYTICAL TEST METHODS FINALIZED

A fully validated stability indicating assay and impurity profile is finalized *prior* to executing the pivotal batch. The analytical methods need to be authorized and signed *prior* to the date of the actual pivotal manufacture.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

PIVOTAL LOTS

Based on the PQ batch results and *amended* documentation, the pivotal lot is now prepared. In the manufacture of the Pivotal Batch, a minimum of 100 000 (*net*) dosage units are required.

Some firms prepare documentation for 100 000 dosage units *gross*, ignoring the fact that there may well be 2% to 5% production losses. The net batch yield turns out to be 98 000 or 95 000 dosage units well below the 100 thousand net required by FDA's Office of Generic Drugs (OGD).

It is prudent to scale the pivotal batch for at least 120 000 dosage units. Remember the pivotal batch may range from 10% net to 100% (i.e. full size) of the proposed commercial batch size.

Experienced Generic firms who do not anticipate any problems with the pivotal documentation often target the pivotal quantity to 70% of the proposed commercial lot thus achieving appropriate scale-up and pivotal in a single batch.

Packing the pivotal batch.

The Pivotal batch needs to be fully packed in the proposed marketing packs (OGD rules). Frequently the pivotal batch is packed into 2, 3 or 4 different pack types and several different pack sizes and closure combinations. (combinations of glass, HDPE, Clicloc™, plastic, metal caps, or Al foil/blister packs etc.)

The tablet trail documentation identifies the exact quantity packed into each container-closure system. The overall packaging should total to 100% of the net pivotal batch.

At least 15-20 % of the exhibition (pivotal) batch should be packed into each container-closure category.

IVIVC FIRST THEN BIOSTUDY

Bioequivalence evaluation

The pivotal batch samples are used to perform the bioequivalent study after an IVIVC has been estimated. The FDA displays a list of about 5-6 model biostudy protocols on specific drug products on the FDA CDER home page.

Where possible consult these protocols with care *prior* to the bioequivalence evaluation.

Pivotal Sampling & Testing

The sampling and testing procedures for the pivotal batch hold a special regulatory significance. The pivotal batch represents the documented batch that is filed with the FDA's Office of Generic Drugs, as well as being the batch representing the therapeutic bioequivalence of the drug product when compared against the reference listed drug (RLD) or the innovator's own drug, during the biostudy. Under these circumstances, the need for a fully representative sampling and testing procedure, as required by GMP, is achieved by a specific written 'sampling and testing' protocol.

This special batch has both legal and regulatory aspects in the eyes of the FDA - sampling must not only be done but seen to be done (i.e. via a well written protocol).

DEVELOPMENT REPORTS

Firms should have a well structured and assembled Product Development Report.

Although **not** a FDA 21 CFR regulatory requirement, a functional Development Report will certainly go a long way to convince the reviewers of a fully justified overall process that consistently produces the desired end-product.

The Development Report is the basis on which the validation protocol is designed and structured, without it validation may well be incomplete or problematic.

Development reports are required to be seen by the site inspectors at the product specific pre-approval inspection (PAI visit). The preparation of a Product Development Report should be based on all the interim reports prepared during the development work, including analytical reports and where well prepared, assembled and structured - oil the review process - immeasurably.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

Locum *International* Publishers
ISSN 0793 8713 - ISSN 0793 8721
A *Series* Publication in association with
The International Association of Generic Drug Manufacturers.

NEW Edition
Year 2000

Handbook of

Pharmaceutical Generic Development

ISBN 965 492 004-2

Part ONE
DRUG Development Know-how
&
Part TWO
ANDA Development Technology

Oral Suspensions

Drug Development

ANDA Development

Cephalosporins
Synthetic Penicillins
Azithromycin
SMX-TMP
(Cotrimoxazole)

The Handbook of Pharmaceutical Generic Development is an essential workbook covering the full CMC & Bio and RA sections of normal **Oral Suspension** ANDA / AADA and a **Suspension for Reconstitution.**

Part One (Development ISBN 965 492 004-2) and **Part Two** (ANDA Development - ISBN 965492005-0 with detailed commercial and state-of-the-art formula) provides essential know-how technology on all aspects of; Development, Formulation, Scale-up, Process Optimization & Qualification; Pivotal and large scale Validation batches; analytical, cleaning and process validation; essential documentation and OGD regulatory know-how that is essential for a successful review for a FDA approval, saving queue-time and money.

Essential development know-how on **Oral Suspensions and Suspensions for Reconstitution** professional developers to understand the nuts-and-bolts on Generic MODIFIED RELEASE DEVELOPMENT with a ***high-tech*** detailed ANDA development to produce flawless files. (Print & CD ROM). Presented at an Advanced Technological Level.

Visit Web Secure Book Shop or Fax+972-97-494 532

handbooks@locumUSA.com

Locum Publishing House PO Box 16075
Arlington VA 22215-1075 USA
Fax Int: +972-97-494 532 / US+(1) 435-808-1891

A Locum House Publication

PRODUCT DEVELOPMENT GUIDE

CONTROLLED RELEASE DOSAGE FORMS

PRE-FORMULATION

Introduction

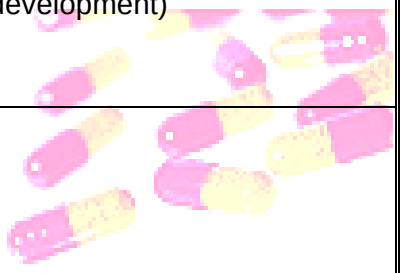
Guidelines for the development of a controlled release product primary for the US market, Note: some tests or procedures may be unnecessary for certain products. The order of performing the various stages may change depending on the product under development. These guidelines may be modified for other geographic zones.

Development	Scope of Product Development Stage
Stage 1	**Literature Search**
Literature Research	USP BP Pharm. Eur, PDR, Martindale, Merck, Florey, Vidal
FDA - FOI	Summary Basis of Approval
On-line computerized search FDA CDER	Electronic Data Base (articles and publication on test methods, Dissolution synthesis procedures, drug impurities, pharmacokinetics and dynamics) Evaluation of Biostudy parameters, Dissolution methods.
Patent evaluation	Orange Guide + FDA CDER WWW Patent Consultant
Stage 2	**Active Sourcing**
Sourcing for Active Raw Material	International Suppliers US, European Asian E.g. Lek (Czech) ZIP, Esteves, (Spain); (Mohrs Spain) (S.I.M Italy) Review Suppliers Catalogues
Potential Suppliers List	Request samples and C of A and Specifications Evaluate at least two suppliers fully.
Stage 3	**Active Evaluation**
Evaluate Potential Actives	Evaluate at least two to three potential active suppliers • DMF availability • Compliance with USP monograph • Impurity profile and stability • Potential Polymorphic / solvate forms • Commitment for physical specifications • Statement of non-patent infringement
Stage 4	**Active Purchasing**
Purchase (Potential) Active Material	Evaluate at least two potential active material suppliers for approved supplier status
Stage 5	**Active Testing**
Testing of Active Material sample	Chemical testing by the R&D analytical lab as per a. Pharmacopoeia monograph (if present) b. Pharmacopoeia Forum (if available) c. In-house method (based on manufacturer) d. Supplier's test methods and specifications

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

FORMULATION

Development	Scope of Product Development Stage
Stage 6	**Innovator's Product Purchasing**
DRUG PRODUCT Innovator Samples	Purchase at least 3 different lots in smallest and largest pack size for each product strength
Stage 7	**Innovator's Product Testing**
Innovator Testing	Evaluate physical parameters:- Tablet shape, tablet color, code for punch embossing, pack sizes containers materials, closure types; cotton and desiccants.
Innovator Physical Testing	Physical testing Weight; Thickness; Hardness; LOD; Friability; Disintegration: Evaluation of tablet punch; size; score; embossing and shape
Evaluation of Innovator formula ingredients	Summary Formula in PDR; International PDRs (Italian, French, Swiss) and Innovators product's insert (obtain latest FOI -FDA) Perform actual analytical testing on innovator's product
Microscopic observation	Particle/crystal information on:- • Particle size • Crystal shape, habit, Differentiation on the presence of specific excipients can be verified from microscopic observation. E.g., Cross-linked cellulose's Starch and Avicel have a specific shapes and morphology
Evaluation of Biostudy parameters	Review FDA CDER Home page for listing and Biostudy parameters Developing a meaningful IVIVC on a product -by-product-basis
Dissolution profile IVIV Correlation	USP monograph and FDA method - (where present) Dissolution; 12 unit Dissolution Profile
Stage 8	**Bulk Active Testing**
FIRST BATCH FROM APPROVED SUPPLIER Full Physical characterization	Physical characterization of bulk batch • Polymorphism • B.E.T. • Particle size distribution (& method development) • Bulk density; • Microscopic observation
FULL CHEMICAL CHARACTERIZATION	Chemical characterization • Assay • Stressed Analysis • Degradants (Expected) • Impurity profile • Optical rotation • Enantiomeric purity • O.V.I. Testing



ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

DEVELOPMENT BATCHES

Development Stage	Scope of Product Development
Stage 9	**Excipients**
Evaluation of formulation with suitable excipients	Choice of Releasing and Non-releasing controlling excipients Evaluating predictability models. Excipient compatibility using DSC methods and stability assessment Choosing dissolution parameters (sampling times and percentage dissolved ranges) Determining several dissolution profiles during formulation; optimization; final formula & process qualification
Stage 10	**Container Closure System**
Evaluation of suitable Container-Closure System	Choice of container-closure-liner system including: • material composition, • type of thermoplastic resin and resin pigments, • manufacturers and suppliers, • liners and seals used by closure manufacturer, • cotton and desiccants. • manufacturer's DMF numbers for all component parts • Letters of Access for regulatory authorities to view DMF dossiers
Stage 11	**Manufacturing Process**
EVALUATION SUITABLE MANUFACTURING PROCESSES Wet Granulation Dry Granulation Slugging and Dry Granulation	• Wet granulation (aqueous or non aqueous) high shear mixing / low shear mixing • FBD spray procedure), or • Dry mixing, dry granulation and/'or Slugging • Determination of order of mixing • Determination of pre-mixing (in Granulator) • Determination of fluid addition (spray rates, if relevant) • Determination of granulation time (chopper I & II) • Determination of torque end-point value • Determination of Drying parameters • Determination of LOD limits • Determination of testing temperature for checking LOD limits (State machine used e.g. Mettler™, Computrac™).
GRANULATION Physical Properties of Granulate	• Flow properties • Density, (bulk; tapped) • Particle-size distribution • Compressibility (Carr's Compression index)
Compression Physical Properties of Compressed Tablets	• Weight, • Hardness, • Thickness, • Friability • Disintegration • Dissolution
Final Formula Established	Assessment of Final Master Formula and accelerated 1-3 month stability profile

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

ACTIVE PURCHASE

Stage 12	Bulk Active Purchased
Active material Bulk purchase	Ordering of Active material for Process Qualification (PQ) and Pivotal Batch(es). On approval of final formula, order sufficient material for the PQ (2) and Pivotal Lots (sufficient for all strengths and batch sizes). NB: Never active mix batch numbers in PQ & Pivotal Lots.

FULL LABORATORY EVALUATION

Development	Scope of Product Development
Stage 13	**Analytical Evaluation**
Analytical testing of tablets/Caplets	• Dissolution - in USP medium (Multipoint profiles) and other relevant media versus Innovator's product. • U of C-for low active concentrations. Refer to USP requirements for uniformity of content vs. uniformity of dosage units.
Dissolution Validation	• Validation Of Dissolution Method; With Choice Of All Discriminatory Dissolution Parameters (Usp Type; Media; Ph; Agitation) Completed Prior To Process Optimization And Process Qualification NOTE: Dissolution parameters (as above) may well be adjusted to establish a Level A or C correlation after IVIV study
Validation Package	• Validation of analytical package i.e. Assay; Dissolution ; Content Uniformity completed prior to Process Qualification

PROCESS OPTIMIZATION

Development	Scope of Product Development
Stage 14	**Process Optimization**
GRANULATION OPTIMIZATION	◊ Effect of granulation parameters ◊ Granulation time, ◊ Speed of choppers (I & II) or mixer blades ◊ Solvent addition rate and overall amount ◊ Ratio of intra-granulate Disintegrant and binders agents ◊ Screen size for milling (e.g. 0.6 or 0.8mm) ◊ Evaluation of optimized granulate and tablet attributes
DRYING BLENDING COMPRESSION	♦ FB Drying temperature vs. target LOD and range limits. Effect on granulate and tablet properties (re: flow, capping, sticking). ♦ Blending times ♦ Lubricant Split into two parts (pre-blending and final blending) ♦ The effect on Content Uniformity, Granule lubrication and Dissolution profile. ♦ Evaluation of unit dose sampling vs. Content Uniformity. ♦ Effect of hardness on tablet - aging, dissolution, friability. ♦ Evaluation of Hardness Range Limits ♦ Evaluation of stability results of optimized mfg. process.
PROCESS OPTIMIZATION REPORT	Prepare PO Report. This Process_Optimization Report forms part of the product Development Report. Dissolution Report included.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

DISSOLUTION PROFILING

Development	Scope of Product Development
Stage 15	**Analytical Evaluation**
Analytical testing of tablets/Caplets	• Dissolution - in USP medium (Multipoint profiles) and other relevant media versus Innovator's product. • U of C-for low active concentrations. Refer to USP requirements for uniformity of content vs. uniformity of dosage units.
	• Validation of analytical package i.e. Assay; Dissolution ; Content Uniformity completed prior to Process Qualification

ESTABLISHING AND INVITRO INVIVO CORRELATION

Development	Scope of Product Development
Stage 16	**Analytical Evaluation**
IVIV Correlation	• Dissolution - in USP medium (Multipoint profiles) and other relevant media versus Innovator's product. • Perform IVIV Bioavailability Study
	Establish a Level A or C correlation without adjusting dissolution parameters and time scale
	• Adjust the dissolution parameters or time scale to achieve a Level A or C correlation (adjust only if necessary)

SCALE UP

Development Stage	Scope of Product Development
Stage 17	**Scale-up**
Scale-up	Scale-up lot prepared if larger batch size scale up problems anticipated.
	Process Qualification batch and Scale-up batch may be evaluated as a single batch.
Scale-up Report	The preparation of a Scale-up Report. The Scale-up report forms part of the overall Development Report

PROCESS QUALIFICATION

Development Stage	Scope of Product Development
Stage 18	**Process Qualification (PQ)**
The process qualification batch is manufactured in order to detect any problems that may arise during the manufacture of production size batches, allowing a solution prior the manufacture of the pivotal demonstration batch. Scale-up to the pivotal batch size or 70% of the pivotal batch may be combined with qualifying the manufacturing process At this stage full manufacturing documentation is prepared alone standard procedures.	

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

PROCESS QUALIFICATION

Development Stage	Scope of Product Development
Stage 18	**Process Qualification - (Continued)**
PRODUCTION FACILITIES	Process Qualification batch should be compressed in a production (production type with same principle & operation) tabletting machine
BATCH SIZE	Size of pivotal and marketing batch confirmed (NLT 100 000 net/ packed at *target* parameters or 10% of proposed market batch).
BATCH DOCUMENTATION	Preparation of Master Formula and Processing Instructions Discussion of formula, manufacturing process and control parameters with production personnel and QA Staff
FINAL REVIEW and AUTHORIZATION	Review of proposed formula, manufacturing process and control parameters with production personnel and QA Staff with authorization signatures (RD; QA-QC; RA; and Production)
PROTOCOL	PQ. protocol prepared
KEY STEPS	Critical manufacturing steps designated; sampling and testing parameters specified.
OPERATING CONDITIONS	Presence of production and control personnel during PQ manufacture
DISSOLUTION PROFILE	12 POINT DISSOLUTION profile of PQ batch.
PROCESS QUALIFICATION REPORT	Upon completion prepare P-Q Report. This P-Q report forms part of the overall Development Report

PIVOTAL BATCH

Development	Scope of Product Development
Stage 19	**Pivotal Production**
PRODUCTION FACILITIES	Pivotal batch MUST be compressed in a production tabletting machine (or production type with same principle and operation)
BATCH DOCUMENTATION	Preparation of FINAL Master Formula and Processing Instructions
REVIEW and AUTHORIZATION	Review of FINAL formula, manufacturing process and control parameters with production personnel and QA Staff. Pivotal authorization signatures (RD; QA-QC; RA; and Production) attached.
OPERATING CONDITIONS	Operation of production and control personnel during Pivotal manufacture, aided by development team.
	The preparation of a Pivotal Report. This pivotal report forms part of the overall Development Report.

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

BIOEQUIVALENT STUDY

Stage	Scope of Product Development
Stage 20	**BIOSTUDY Evaluation**
BIOSTUDY	Perform Food Effect AND Fasted Biostudy on Pivotal Lot Samples
HIGHEST DOSAGE	Biostudy generally performed on highest strength of product
TWO STUDIES	Food Effect AND Fasted Study required for CR/MR/ER forms
WAIVER CONDITIONS	For multiple strength CR products Invitro dissolution testing conducted in three different pH media on lower dosage forms
SIMILARITY TESTING	Perform Similarity Test [F_2 Test] on dissolution results

PRE-SUBMISSION AUDITING

Stage	Scope of Product Development
Stage 21	**ANDA Pre-Submission Auditing**
Development Report	Audit all raw data supporting Development Report
ANDA Regulatory File	Audit Plant and Laboratory Documentation as per ANDA
SOPs	Review SOP System and Update level
CGMP	Review cGMP of Manufacturing Processes
Validation Protocol	Product Process Validation Protocol complete and signed
Biostudy Report	Evaluate and develop a IVIV correlation (Level A where possible)

ANDA SUBMISSION

Stage	Scope of Product Development
Stage 22	**ANDA Submission**
ANDA Submission	Submit ANDA after thorough in-house audit review
	Biostudy Section 6 (Separate File)
	(9 Copies - as per Color system)
	(1 Field Copy)

VALIDATION BATCHES

Stage	Scope of Product Development
Stage 23	**Process Validation**
Protocol	Process Validation Protocol for 3 consecutive marketing lots
Execute validation	Process Validation of 3 consecutive marketing lots
Report	Process Validation Report
Similarity	Show intra-batch similarity
Bio-Validation Similarity	Show inter-batch similarity between Biobatch (Pivotal) and the Commercial Validation Lots

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

COMMERCIAL RE-VALIDATION DUE TO MAJOR CHANGE

Stage	Scope of Product Development
Stage 24	**Process Re-validation**
Formula Change	Revalidate procedure with new formula process or equipment with
Process Change	a different operating principle
Equipment Change	Follow SUPAC **MR** Rules Level I, II or III
Minor change	Follow SUPAC **MR** Rules Level I

IMPORTANT NOTE ON DEVELOPMENT

Developers are encouraged to develop IVIVC for CR/ER dosage forms in the expectation that the information will be useful in establishing dissolution specifications and will permit certain post approval formulation and manufacturing changes without additional bioequivalence studies.
The objective of developing an IVIVC is to establish a predictive mathematical model describing the relationship between invitro dissolution settings and the actual invivo drug-plasma parameters found, (AUC, C_{max}, T_{max}).

The invitro dissolution settings are adjusted (via media, pH agitation) until a I : I correlation is achieved (Level A) or a single dissolution point and a plasma parameter is shown to correlate (Level C). When more than one point correlates a multiple Level C is obtained - which may possibly be upgraded to a Level A with additional work.
This matching of dissolution settings with plasma levels, that are derived from a specific CR formula and its corresponding manufacturing process, is in fact simply an arbitrary set of values that establish the so called 'predictive mathematical model'.

An IVIVC should be evaluated to demonstrate that predictability of the invivo performance of the drug product (plasma parameters) from its in vitro dissolution characteristics (equipment settings) is maintained over a range of dissolution release rates and manufacturing changes.

DEFINITIONS.

MR Modified Release Solid Oral Dosage Forms include both delayed and extended release drug products

ER Extended Release Dosage Form: A dosage form that allows a *reduction* in dosage frequency as compared to that presented by conventional dosage forms such as a solution or an immediate release dosage form

DR Delayed Release The release of a drug at a time other than immediately following oral administration

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

STANDARD OPERATING PROCEDURES

SOP # HPGD-02-Y2K

CR FORMULA DEVELOPMENT

The following selected model Standard Operating Procedures are recommended for a controlled release development unit:

DEVELOPMENT SOPs

HPGD-02-Y2K Setting up a *Product Specific* **ER** Development SOP.

HPGD-02-Y2K Setting up IVIVC for **E**xtended **R**elease *Oral Dosage Forms*

HPGD-02-Y2K Contents of a Development SOP - **ER** Oral Tablets.

DEVELOPMENT FORMULA

HPGD-02-Y2K Formulation of CR / ER[1] ANDA Oral Tablet Preparations

HPGD-02-Y2K Establishing an IVIVC in Extended Release *Oral Dosage Forms*

HPGD-02-Y2K Standard Procedures for Generic Product Development

HPGD-02-Y2K Establishing a level A IN-VITRO IN-VIVO correlation

HPGD-02-Y2K Establishing a level B IN-VITRO IN-VIVO correlation

HPGD-02-Y2K Establishing a *standard* level C IN-VITRO IN-VIVO correlation

HPGD-02-Y2K Establishing a *multiple* level C IN-VITRO IN-VIVO correlation

DEVELOPMENT REPORT

HPGD-02-Y2K Evaluating the predictability of a level A - IVIV Correlation

HPGD-02-Y2K Development and Evaluating of a level C IVIV Correlation

[End of Document

Edition No. : 01	Effective Date:	APPROVED:
Ed. Status New	DD/MM/2000	_____ _____ _____ _____/_____ Department RD RA QC / Q A

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

It will take you awhile
to cover this unique drug development archive...

ISSN 0793 694X US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 Pacific Rim

Vitro-In-Vivo

U. of Maryland & IAGIM

IVIVC Series Part I

Correlations

In Vitro In Vivo Correlation with Metoprolol Extended Release Tablets Using Two Different Releasing Formulations: An Internal Validation Evaluation

Author:- Natalie D. Eddington[1,2*] [1]Pharmacokinetics Bio-pharmaceutics Laboratory [2]Department of Pharmaceutical Sciences School of Pharmacy, University of Maryland at Baltimore 100 Penn Street, AHB Baltimore, MD 21201-6808 (410)706-6710 (410)706-6580-(fax) Email: neddingt@rx.umaryland.edu

Summary/Abstract

The objective of this analysis was develop and validate internally an in-vitro in-vivo correlation (IVIVC) for a hydrophilic matrix extended release metoprolol tablet using a combination of two formulations with different release rates. Three formulations of a hydrophilic matrix extended release tablet were manufactured to release metoprolol at a slow, moderate and fast rate. The in vitro dissolution methods utilized USP Apparatus II, pH 6.8 at 150 rpm.

Seven healthy subjects received three metoprolol formulations (100 mg): **slow, moderate, fast** releasing and an **oral solution** (50 mg).

Serial blood samples were collected over 48 hours and analyzed by a validated HPLC assay using fluorescence detection. The f_2 metric (similarity factor) was used to analyze the dissolution data.

Correlation models were developed using pooled fraction dissolved (FRD) and fraction absorbed (FRA) data from various combinations of two formulations (slow/moderate; moderate/fast and slow/fast).

Predicted metoprolol concentrations were obtained by convolution of the in vivo dissolution rates. Prediction errors were estimated for C_{max} and AUC to determine the validity of the correlation.

An average percent prediction error for C_{max} and AUC for all formulations of less than 12% was found for all IVIVC models. The relatively low prediction errors for C_{max} and AUC observed strongly suggest that the metoprolol IVIVC models with two formulations used in development are valid.

Previous IVIVC with all three formulations was also found to be valid. The relatively low prediction error indicates that the correlations are predictive when using two or three formulations, and allows the associated dissolution data to be used as a surrogate for bioavailability studies.

Introduction

The process of developing and validating an in vitro in vivo correlation (IVIVC) is playing an exceedingly prominent role in the formulation of extended release products.

The development and validation of IVIVCs has been discussed extensively over the past 10 years. The focus of the debates center on the processes of developing an IVIVC and methods to assess its validity.

Even though there are numerous examples of IVIVCs in the literature, many of the correlations have not been rigorously tested through a systematic evaluation of their predictability.

A validated IVIVC allows for the prediction of the in vivo behavior of alternative formulations, provided that

ISSN 0793 694X - US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 - Pacific Rim

the "new" formulation is within a predefined range determined by the formulations used to develop the correlation.

In addition, the identification of an appropriate dissolution testing system is critical in IVIVC development and subsequent validation, since it provides the link between dosage form optimization and the oral absorption profile.

The recent FDA-IVIVC guidance, outlines methods of internally and externally validating an IVIVC along with the predictive criteria to assess its validity.[1]

Internal validation refers to how well the IVIVC model predicts the in vivo behavior of the formulations used to develop the correlation.

External validation focuses on how well the IVIVC model predicts the bioavailability of alternative formulations, which differ from those, used in the initial correlation.

The alternative formulations may represent changes in release and non-release controlling excipients, manufacturing site changes, and manufacturing process changes or scale-up of a formulation.

Previous work in our laboratory has focused on the influence of processing changes, excipient changes and scale-up on in vitro dissolution and in vivo bioavailability.[2,3]

Further extension of this work examined the development and internal validation of a matrix metoprolol extended release dosage form.[4]

Numerous sustained or extended release metoprolol formulations have been previously developed, however there are limited examples of validated IVIVCs for metoprolol.

Previously, an IVIVC was developed and validated for a hydrophilic matrix extended release metoprolol formulation.

The IVIVC was developed using three formulations of metoprolol tartrate as well as various combinations of the three formulations.

According to the Biopharmaceutics Classification System, metoprolol is a "Class I" drug, i.e. high solubility and permeability.[5]

In addition, its relatively short half-life suggests that it is a suitable candidate for an extended release formulation. In previous work, we have developed and validated a correlation for extended release metoprolol tablets using three different releasing formulations.

The IVIVC guidance suggests that a correlation can be developed with two or three formulations. The purpose of this work is to assess the ability of developing a correlation with metoprolol extended release formulations using various combinations of two formulations.

METHODS

Formulations. Metoprolol formulations evaluated in this analysis have been previously described.[4]

Three formulations were designed to release metoprolol at a slow, moderate and fast rate. The formulations were manufactured at the Industrial Pharmacy Laboratory at the University of Maryland using hydroxypropyl-methylcellulose (HPMC) as the release rate controlling excipient.

The formulations were designed to release metoprolol at three different rates referred to as: **slow, moderate** and **fast**.

Dissolution.

The release characteristics of the slow, moderate and fast formulations were examined using the following dissolution testing methodologies: USP Apparatus I, pH 6.8 at 150 rpm.

ISSN 0793 694X - US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 - Pacific Rim

Dissolution tests were performed on six tablets and the amount of drug released was analyzed spectophotometrically at a wavelength of 275nm. Dissolution samples were collected over a 12 hour period.

Bioavailability Study:

The Bioavailability Study has been previously reported.[4] This was an open, fasting, single dose, four treatment crossover study. The health status of each subject was based on physical examination, history, ECG and clinical laboratory tests.

Nine normal healthy, male and female, non-smoking volunteers were enrolled in the study and received three formulations of metoprolol (100 mg) in a randomized fashion. In addition, to the extended release formulations, an oral solution (50 mg) of metoprolol tartrate was also administered.

Blood samples (6 ml) were collected at the following times: 0 (pre-dose) and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, and 24 hours post-dosing. Samples were centrifuged for 10 minutes at 25oC. Each metoprolol administration was separated by a washout period of seven days. Pulse rate and blood pressure were monitored in each subject at least three minutes prior to each blood sample collection.

The study was approved by the University of Maryland and the Baltimore Veteran's Administration Institutional Review boards and each subject provided informed consent prior to enrollment.

Metoprolol plasma sample analysis was performed with a previouly validated HPLC fluorescence detection method.[6]

Dissolution Data Analysis.

The in vitro dissolution data was analyzed by estimation of a similarity factor, the f_2 metric[7] and parameterized by the sigmoid Emax model.

The dissolution profiles were compared using the similarity factor, f_2, presented in the following equation (1):

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

Where R_t and T_t are the percent dissolved at each time point for the reference product and the test product, respectively.

Using the f_2 values, dissolution profiles were considered dissimilar if these values were less than 50 with the average difference between any dissolution samples not being greater than fifteen percent.

In Vivo Data Analysis.

Metoprolol concentration-time data was evaluated using the Phast program*. The bioavailability parameters, C_{max}, T_{max} and AUC_{inf} were estimated for each subject. (*Phoenix Scientific Software, Version 2.2, Montreal, Canada) and WINNOLIN Professional (SCI Software; Cary, North Carolina)

The percent of drug absorbed versus time was determined using numerical deconvolution, where the pharmacokinetic parameters of the oral solution were used as the impulse function.

Correlation Development and Internal Validation.

The data generated in the bioavailability study was used to develop the IVIVC.

The correlation was developed using mean metoprolol plasma concentration vs. time data following the slow, moderate and fast releasing formulation.

The correlation models was developed using pooled mean FRD and pooled mean FRA data from the following combinations of two formulations: (1) slow and moderate (S/F), (2) moderate and fast (M/F) and (3) slow and fast (S/F). Linear regression analysis was used to examine the relationship between FRD and FRA.

The internal validation was based on how well each IVIVC model (S/M, M/F and S/F) predicted the in vivo performance of each formulation (i.e., slow, moderate and fast).

The in IVIVC model predicted metoprolol plasma concentration was determined by convoluting the in vivo dissolution rate with the pharmacokinetic parameters from the oral solution administration.

The validity of the three correlation models (S/M, M/F or S/F) was determined by calculating the prediction errors for the observed and predicted C_{max} and AUC for each formulation to determine the accuracy of the IVIVC models in characterizing the rate and extent of metoprolol absorption.

The percent prediction errors for C_{max} and AUC were calculated as follows:

(2) - $\%PE_{Cmax}$

$$= \left[\frac{[C\max(obs) - C\max(pred)}{C\max(obs)}\right] * 100$$

(3) - $\%PE_{AUC}$

$$= \left[\frac{[AUC(obs) - AUC(pred)}{AUC(obs)}\right] * 100$$

KEY

Where C_{max}(obs.) and C_{max}(pred.) = The observed and IVIVC model predicted maximum plasma concentration profiles, respectively;

AUC(obs.) and AUC(pred.) = The observed and IVIVC model predicted AUC for the plasma concentration profiles, respectively.

The IVIVC was considered valid if the C_{max} and AUC prediction errors were $\leq$ 10 percent.[1]

RESULTS

In vitro and in vivo studies.

Profiles of the cumulative metoprolol fraction dissolved from the slow and moderate (S/M), moderate and fast (M/F) and slow and fast (S/F) formulations using USP Apparatus I, pH 6.8, 150 rpm are illustrated in **Figure 1A, 2A and 3A**, respectively.

The associated f_2 metrics for the S/M, M/F and S/F were found to be 39.26, 45.99 and 30.9 respectively, which suggested that the two profiles were not similar.

Mean pharmacokinetic parameters are summarized in **Table 1.**

Table 1. Mean Pharmacokinetic Parameters after Extended Release Metoprolol Formulations.

Formula Type	C_{max} (mg/L)	T_{max} (hrs)	AUC_{inf} (mg.hr/L)
Solution	58.6 (13.8)	2.07 (0.53)	346 (40.6)
Slow	66.2 (15.4)	4.86 (1.06)	718 (192)
Moderate	91.0 (32.5)	3.57 (0.53)	810 (287)
Fast	120 (31.5)	3.14 (0.38)	821 (197)

Figures 1B – 3B:-

Present the fraction of drug absorbed for the slow and moderate (S/M), moderate and fast (M/F) and slow and fast (S/F) formulation vs time.

IVIVC Correlation, Development and Validation.

Figures 4A - 4C present the pooled FRD vs. FRA for the S/M, M/F and S/F formulations using USP Apparatus I, pH 6.8 at 150 rpm.

The regression lines obtained between FRA and FRD for all IVIVC models were significant ($p < 0.05$) and the slopes were not significantly different from 1 ($p < 0.05$).

The internal validation was performed by convolution of the (S/M, M/F and S/F) dissolution data that corresponded to each formulation (S/M/F). Each of the IVIVC models predicted metoprolol plasma concentration versus time profiles was compared to the experimental data points using prediction error metrics.

Figure 5, 6 and 7 illustrate the observed and IVIVC model metoprolol plasma concentrations for each formulation using the S/M, M/F and S/F IVIVC models, respectively.

The validity of the correlations was assessed by determining how well the IVIVC models could predict the rate and extent of metoprolol absorption as characterized by C_{max} and AUC.

Table 2 presents the percent errors estimated for the difference between the observed and predicted C_{max} and AUC values for the S/M, M/F and S/F IVIVC models.

Table 2. Regression Parameters for IVIVC Models of Metoprolol

IVIVC Models

Formula Types	Slope	Intercept	r	P value
S/M	1.171	-0.191	0.991	p <0.001
M/F	1.207	-0.276	0.966	p <0.001
S/F	1.131	-0.203	0.946	p <0.001

None of the model predicted parameters deviated from the experimental values by more than twelve percent (12%).

DISCUSSION

The availability of a meaningful IVIVC of high quality and predictability for an extended release formulation should provide a sound foundation for product optimization.

An established IVIVC allows for certain post-approval changes as described in the Scale-up and Post Approval Changes for Modified Release (SUPAC-MR) FDA Guidance.[8]
Further, a valid IVIVC allows for the use of dissolution data in place of additional bioavailability studies.

The objective of this analysis was to assess the development and validation of an IVIVC for metoprolol tartrate tablets using two formulations. Previously, we have internally validated a correlation using a total of three formulations designed to release the drug at a slow, moderate and fast rate.[4]

An average percent prediction error for C_{max} and AUC of less than 10% was found for the IVIVC model developed with all three formulations.

The average percent prediction error of less than 10% indicates that the three-formulation correlation was predictive and allows the associated dissolution data to be used as a surrogate for bioavailability studies.

Our current analysis examined how well two formulations were able to accurately predict the in vivo bioavailability profile of various extended release formulations of metoprolol.

IVIVC models developed with combinations of the slow and moderate, moderate and fast and slow and fast formulations were able to accurately predict the rate of metoprolol absorption from the extended release formulations.

Prediction errors for Cmax were all less than **6%**, except for the slow and moderate IVIVC that displayed an error

of 11.38 % (Table #3). AUC prediction errors were all less than **10%** irrespective of the formulations used to develop the IVIVC suggesting that the IVIVC models also predicted the extent of drug absorption.

According to the IVIVC guidance, the average prediction error across formulations cannot be greater than **10%** and a formulation cannot have a prediction error greater than **15%.** Based on these criteria, each of the IVIVC models is **valid** in terms of the **rate and extent** of drug absorption.

In summary, correlations were developed with combinations of two formulations (e.g. slow and moderate, moderate and fast, slow and fast). The evaluation of the correlation of FRD vs. FRA displayed a significant linear relationship for each of the combinations.

As observed with correlation developed with three formulations, each correlation here was able to accurately estimate the rate as well as the extent of absorption. These results indicate that a predictive correlation can be developed with two or three formulations with this Class I agent and this suggests that similar results may be observed with other agents in this classification.

Table 3.

C_{max} and AUC Prediction Errors (%) for Metoprolol IVIVC

Formulation	Cmax S/M	M/F	S/F
Slow	-11.38	-3.75	-3.75
Moderate	-1.55	5.18	4.25
Fast	-1.83	3.55	5.74
AUC			
Formulation	S/M	M/F	S/F
Slow	-5.77	1.05	1.05
Moderate	1.52	7.07	6.94
Fast	-0.97	3.71	6.25

References & Literature Cited

1. Guidance for the Industry: Extended Release Solid Oral Dosage Forms: Development, Evaluation and Application of In Vitro/In vivo Correlations. U.S. Department of Health, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), July 1997.
2. Rekhi GS, Eddington ND, Fossler MJ and Augsburger LL. Evaluation of In Vitro Release Rate and In Vivo Absorption characteristics of Four Metoprolol Tartrate Immediate Release Tablet Formulations. Pharml Dev Tech. 29(1), 11-24, 1997.
3. Eddington ND, Ashraf M, Leslie JL, Fossler MJ and Augsburger LL. Identification of Formulation and Manufacturing Variables that Influence In Vitro Dissolution and In Vivo Bioavailability of Propranolol Hydrochloride Tablets. Pharmaceutical Dev Tech. 3, 535-547, 1998.
4. Eddington ND, Marroum P, Uppoor R, Hussain A and Augsburger L. Development and Internal Validation of an In Vitro In Vivo Correlation for Hydrophilic Metoprolol Tartrate Extended Release Tablet Formulations. Pharm. Res. 15, 466-473,1998
5. Amidon, G. L., H. Lennernas, V. P. Shah, and J. R. Crison, "A Theoretical Basis For a Biopharmaceutic Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability," Pharmaceutical Research, 12: 413-420, 1995.
6. Mistry B, Leslie J and Eddington, ND.A Sensitive Assay of Metorpolol and its Major Metabolite α-hydroxy Metoprolol in Human Plasma and Determination of Dextromethorphan and its Metabolite Dextrophan in Urine with High Performance Liquid Chromatography and Flurometric Detection J Pharmaceut Biomed Anal., 16, 1041 –1049, 1998.
7. J.W. Moore and H.H. Flanner. Pharm Tech. 6: 64-74 (1996).
8. Modified Release Solid Oral Dosage Form Guidance: Scale-up and Postapproval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation. U.S. Department of Health, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), September, 26, 1997

Editorial correspondence and reprint requests to: Natalie D. Eddington, Ph.D. Pharmacokinetics Biopharmaceutics Laboratory Department of Pharmaceutical Sciences School of Pharmacy, University of Maryland at Baltimore 100 Penn Street, AHB Baltimore, MD 21201-6808 (410) 706-6710 (410) 706-6580 (fax)

EIGHT IVIVC STUDIES in 2000

This article represents the first in the series of **eight** IVIVC reviews by the author in a joint collaboration project with the International Drug Development Association – **IAGIM** Full details of the 12 month joint venture with the **University of Maryland** VA USA and IAGIM can be viewed at: http://www.locum.co.il/future

ISSN 0793 694X - US/Canada ISSN 0793 7784 Euro ISSN 0793 7822 - Pacific Rim

Figure 1.
Mean dissolution and absorption profiles for the **SLOW** and **MODERATE** Formulation:
(A) Fraction of drug dissolved (FRD) and (B) Fraction of drug absorbed (FRA).

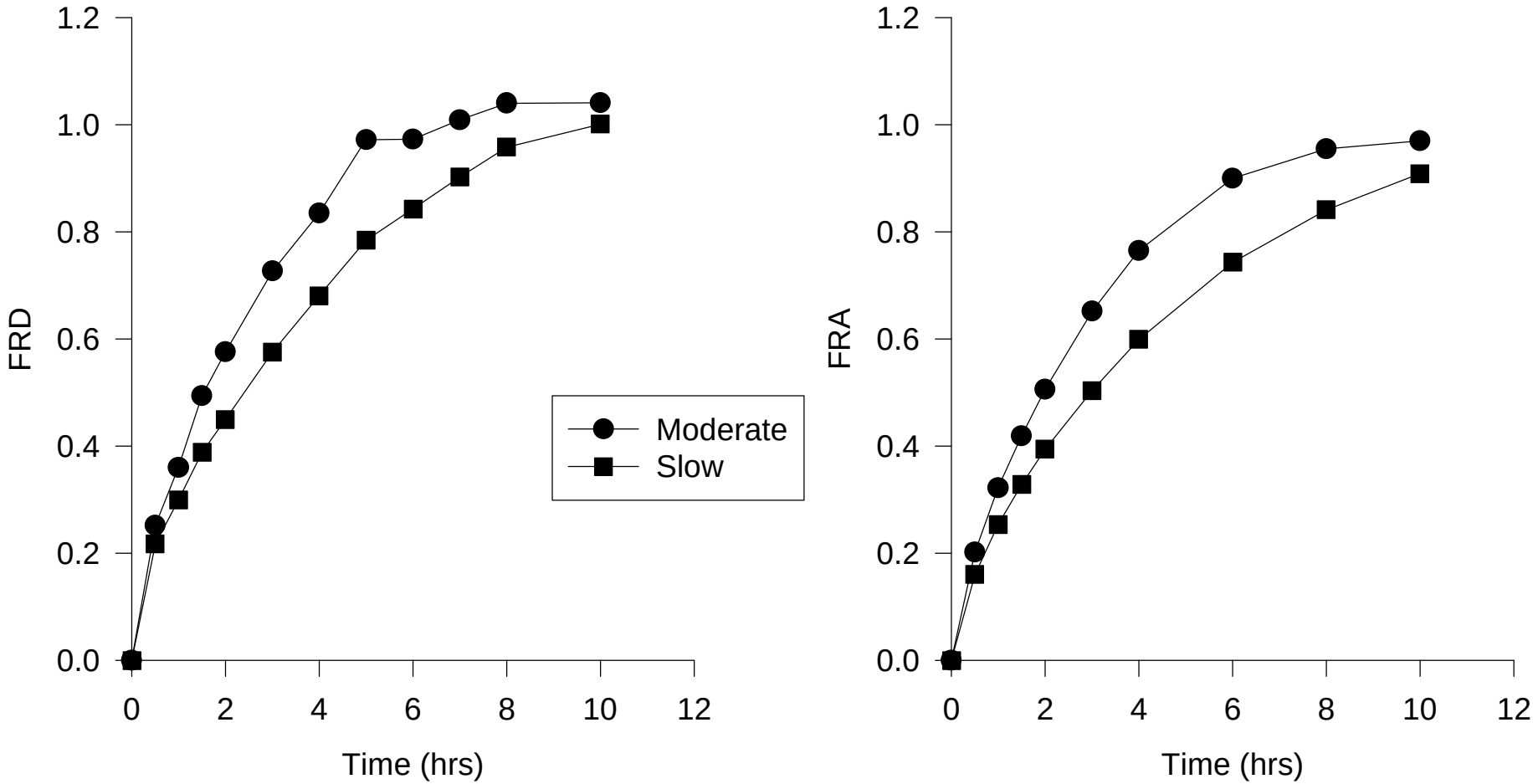


Figure 2. Mean dissolution and absorption profiles for the **MODERATE** and **FAST** Formulation:
(A) Fraction of drug dissolved (FRD) and (B) Fraction of drug absorbed (FRA).

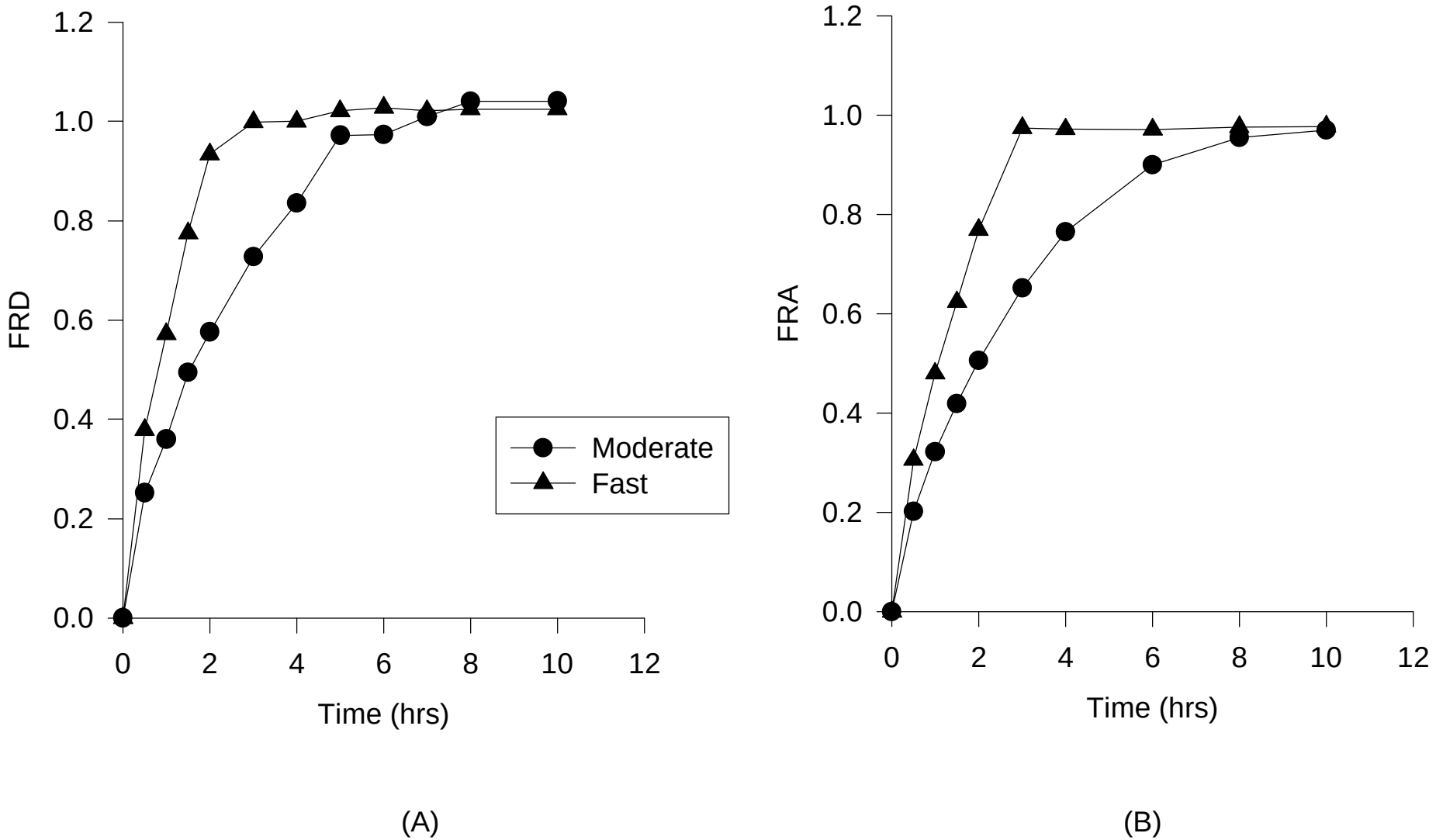


Figure 3.
Mean dissolution and absorption profiles for the **SLOW** and **FAST** formulation:
(A) Fraction of drug dissolved (FRD) and (B) Fraction of drug absorbed (FRA).

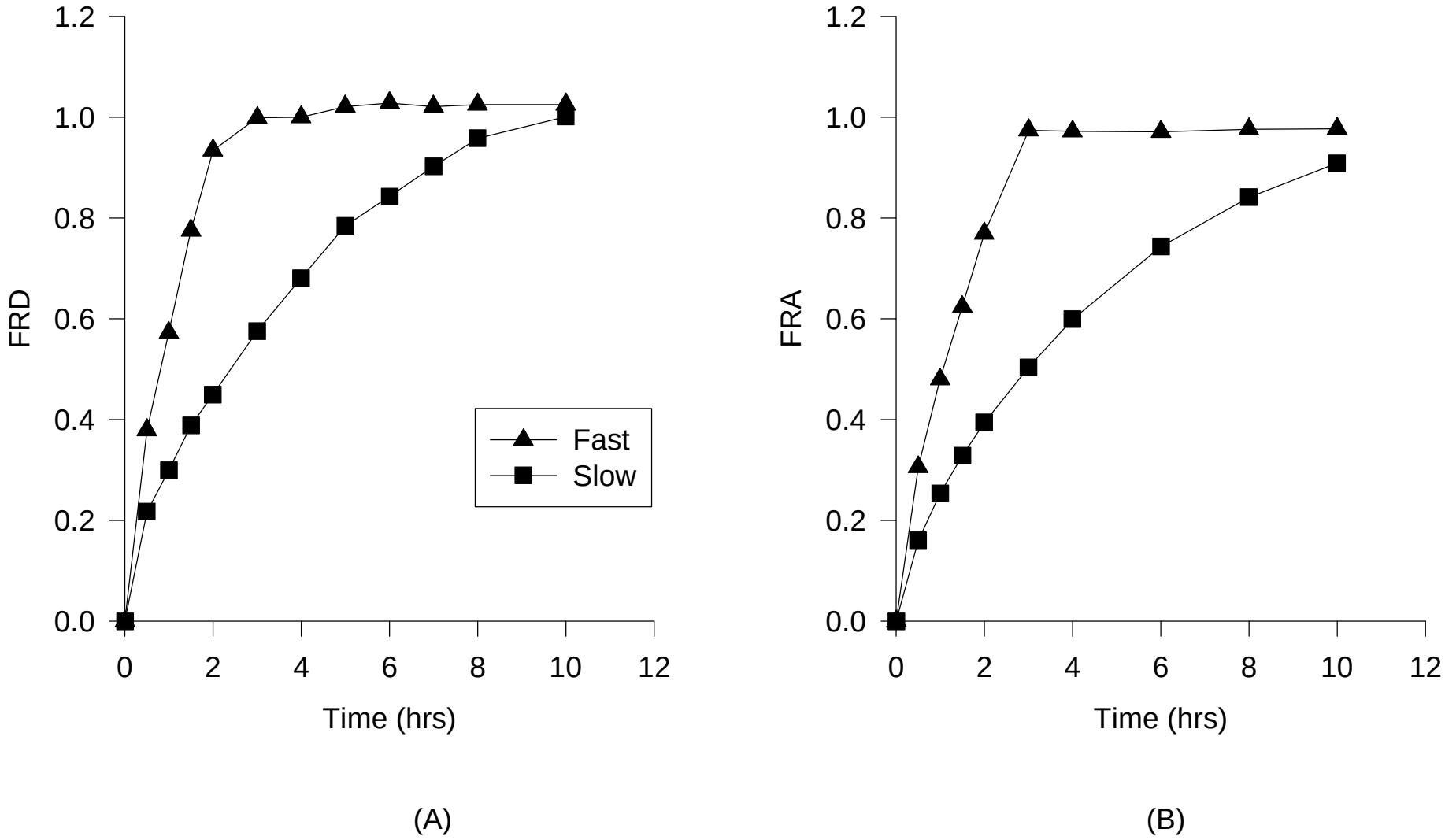


Figure 4.
IVIVC model linear regression plots of FRA vs FRD:
(A) SLOW and MODERATE Formulations, (B) MODERATE and FAST Formulations and (C) **SLOW** and **FAST** Formulations.

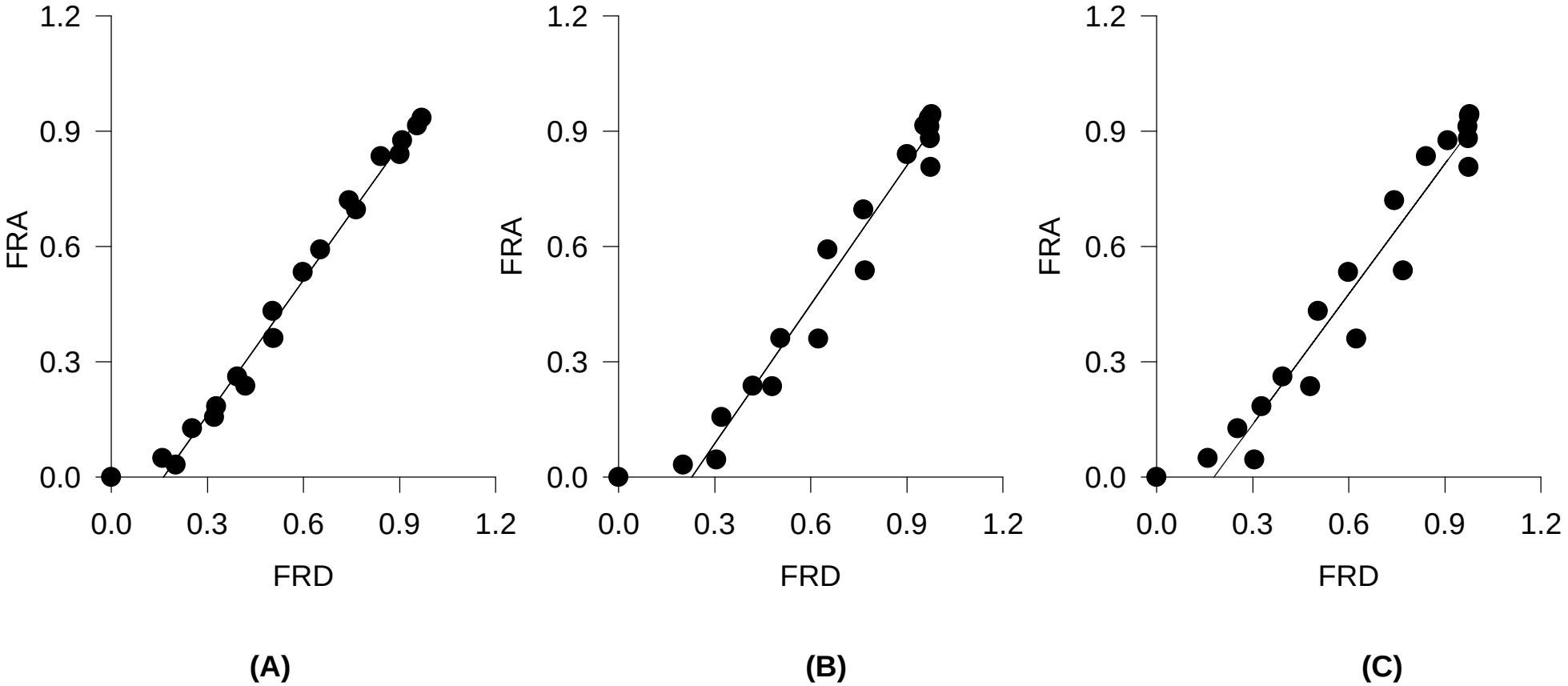


Figure 5.
Observed and predicted metoprolol plasma concentration for the **SLOW** and **MODERATE** IVIVC:
(A) **SLOW** Formulation, (B) **MODERATE** Formulation and (C) **FAST** Formulation.

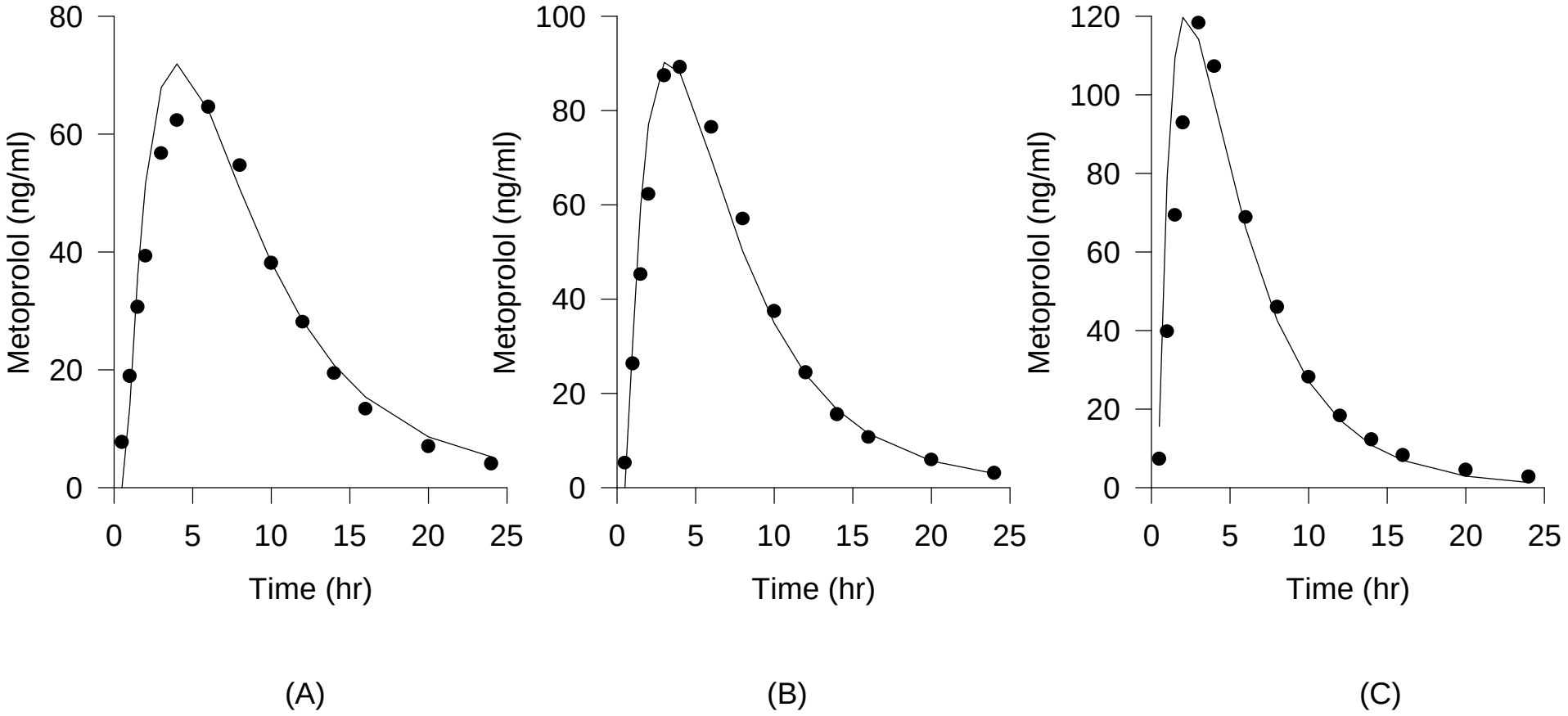


Figure 6.
Observed and predicted metoprolol plasma concentration for the **MODERATE** and **FAST** IVIVC:
(A) **SLOW** Formulation, (B) **MODERATE** Formulation and (C) **FAST** Formulation.

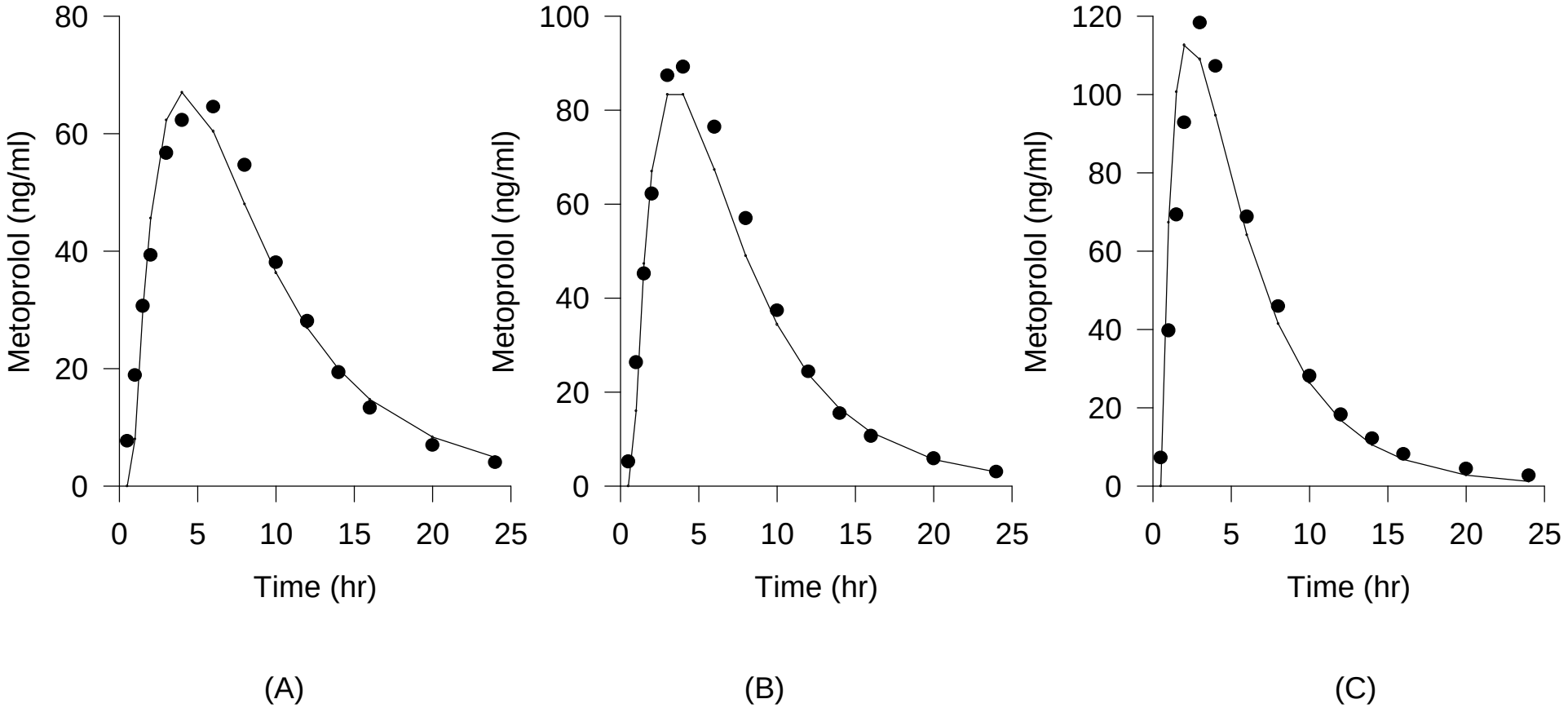


Figure 7.
Observed and predicted metoprolol plasma concentration for the **SLOW** and **FAST** IVIVC:
(A) SLOW Formulation, (B) MODE**R**ATE Formulation and (C) **FAST** Formulation.