GUIDELINE ON THE REVIEW OF BIOEQUIVALENCE STUDIES AND COMPARATIVE DISSOLUTION REPORTS

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NATIONAL MEDICINE REGULATORY AUTHORITY
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GUIDELINE ON THE REVIEW OF BIOEQUIVALENCE STUDIES AND COMPARATIVE DISSOLUTION REPORTS

CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Full Term
AUC	Area Under the Plasma Concentration-Time Curve
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
Cmax	Maximum (Peak) Plasma Concentration
CTD	Common Technical Document
EMA	European Medicines Agency
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Council for Harmonisation
IR	Immediate Release
NMR/NMRA	National Medicines Regulatory Authority
NTID	Narrow Therapeutic Index Drug
PK	Pharmacokinetics
RLD	Reference Listed Drug
SmPC	Summary of Product Characteristics
tmax	Time to Maximum Plasma Concentration

1. INTRODUCTION

This guideline has been prepared by the National Medicines Regulatory Authority (NMRA) of Sri Lanka as a supplementary document to Guideline GL-021 (Guideline on Registration of Medicines) on the Investigation of Bioequivalence. It provides specific guidance to applicants, manufacturers, and regulatory reviewers on the requirements, procedures, and standards applicable in Sri Lanka for the review of Bioequivalence (BE) studies and Comparative Dissolution Reports (CDR) submitted as part of medicine registration applications.

This guideline reflects the NMRA's commitment to ensuring that all medicines registered in Sri Lanka are of proven quality, safety, and efficacy, while promoting access to affordable medicines through a risk-proportionate regulatory framework.

> **NOTE:** *This guideline should be read in conjunction with GL-021 (Guideline on Registration of Medicines, NMRA, SL), the ICH M13A Guideline on Bioequivalence for Immediate-Release Solid Oral Dosage Forms, and other applicable NMRA guidelines and regulations.*

2. SCOPE

This guideline applies to:

- Marketing Authorisation Holders (MAH) for generic and multi-source pharmaceutical products submitted for registration with the NMRA Sri Lanka.
- Domestic manufacturers (those manufacturing within Sri Lanka) and foreign manufacturers.
- Immediate-release (IR) solid oral dosage forms with systemic action (e.g., tablets, capsules).
- Post-approval variation applications where reformulation or manufacturing changes may affect bioavailability.

This guideline does not apply to:

- Inhaled, or parenterally administered products.
- Biological/biosimilar medicinal products.

3. REGULATORY BASIS AND BACKGROUND

The requirement for bioequivalence data as a condition for marketing authorisation of generic medicines is grounded in internationally accepted regulatory science. Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically

equivalent or pharmaceutical alternatives, and their bioavailabilities (rate and extent of absorption) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance in terms of safety and efficacy.

The NMRA Sri Lanka has adopted a risk-proportionate approach, aligned with WHO recommendations and international guidelines (including EMA GL and ICH M13A), to determine the type and level of biopharmaceutical evidence required for each product application. The Biopharmaceutics Classification System (BCS) forms the scientific basis for differentiating study requirements.

4. BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS) AND STUDY REQUIREEMENTS

4.1. Overview of BCS

The BCS classifies drug substances into four classes based on their aqueous solubility and intestinal permeability:

Class	Solubility	Permeability	Key Characteristics
I	High	High	Rapidly dissolving; absorption limited by gastric emptying
II	Low	High	Dissolution rate-limited absorption; formulation-dependent BA
III	High	Low	Permeability-limited absorption; dissolution usually rapid
IV	Low	Low	Poor absorption; both dissolution and permeability are limiting

4.2. NMRA study Requirements Based on BCS Classification

The NMRA requires different levels of biopharmaceutical evidence depending on the BCS classification of the active pharmaceutical ingredient (API), as outlined below.

4.2.1. BCS Class I and Class III Products

For medicines whose API is classified as BCS Class I or Class III, a full in vivo bioequivalence study is generally not required as a primary submission requirement. Instead, applicants must submit a Comparative Dissolution Report (CDR) demonstrating similarity of dissolution profiles between the test product and the selected comparator product.

NOTE: *For BCS Class I and III products with a Narrow Therapeutic Index , a bioequivalence study is not required when safety and effectiveness can be adequately monitored.*

4.2.2. BCS Class II and Class IV Products

For medicines whose API is classified as BCS Class II or Class IV, a full in vivo bioequivalence study conducted in accordance with GL-021 and this guideline is required before registration can be granted. These classes present greater risk of bioavailability variation due to formulation and manufacturing differences, and in vitro dissolution testing alone is generally insufficient as a surrogate.

5. REGISTRATION PATHWAY : DOMESTIC vs. FOREIGN MANUFACTURERS

5.1. Foreign Manufacturers

Foreign manufacturers (those manufacturing outside Sri Lanka) must submit a complete and validated in vivo BE study report for BCS Class II and Class IV products as part of the initial marketing authorisation application. There is no provision for provisional registration based on a comparative dissolution report for foreign manufacturers of BCS Class II or Class IV products.

Requirement:
Foreign manufacturers of BCS Class II/IV products: Full BE study report is mandatory for registration.

5.2. Domestic Manufacturers

Recognising the developmental challenges faced by domestic (Sri Lanka-based) pharmaceutical manufacturers, the NMRA has established a provisional registration pathway that allows domestic manufacturers to commence the registration process with a Comparative Dissolution Report (CDR), provided the following conditions are satisfied:

1. The applicant submits a complete and acceptable Comparative Dissolution Report (CDR) comparing the test product against an NMRA-accepted comparator product.
2. The applicant submits a Declaration Letter (see Section 5.2.1) committing to conduct and submit a full in vivo BE study within the timeframe specified by the NMRA.
3. The CDR and Declaration Letter are submitted alongside the full marketing authorisation dossier.

5.2.1. Declaration Letter Requirements

The Declaration Letter must be submitted on company letterhead, signed by the authorised signatory (e.g., Managing Director or Head of Regulatory Affairs), and must include:

- Full product name, strength(s), and dosage form.
- BCS classification of the API, with supporting references.
- A commitment to conduct a full in vivo BE study in accordance with GL-021 and this guideline.
- A proposed timeline for completion and submission of the BE study report
- Acknowledgement that full registration is conditional on successful submission of an acceptable BE study report.
- Confirmation that the BE study will use a batch representative of the to-be-marketed product.

> **NOTE:** *Provisional registration will not be converted to full registration until an acceptable BE study report is submitted and approved by the NMRA. The NMRA reserves the right to withdraw provisional registration if the BE study report is not submitted within the committed timeline.*

5.2.2. Summary: Domestic Manufacturer Pathway for BCS Class II/IV

Stage	Submission Required	Outcome
Stage 1 (Initial)	Full CTD dossier + CDR + Declaration Letter	Provisional Registration
Stage 2 (Within agreed timeline)	Full in vivo BE Study Report	Full Registration

6. SELECTION OF COMPARATOR PRODUCT

The selection of an appropriate comparator product is critical to ensure that bioequivalence data are clinically meaningful and will allow extrapolation to the intended patient population. The NMRA accepts the following categories of comparator products, in order of preference:

6.1. Priority Order for Comparator Product Selection

Priority	Category	Description and Criteria
1st	Innovator/Originator Product	The original brand product approved on the basis of full clinical, preclinical and quality data. This is the preferred comparator as it has the most complete pharmacological and clinical characterisation. The batch used should meet assay content requirements (not differing by more than 5% from the test product batch).
2nd	Reference Country Product	A product registered and marketed in a country identified by the NMRA as a reference country (e.g., USA, EU member states, UK, Japan, Canada, Australia). Applicants must confirm

Priority	Category	Description and Criteria
		that the product is the innovator or an accepted reference product in the reference country.
3rd	Market Leader Product	The product with the highest market share in Sri Lanka for the same active substance, strength, and dosage form. This option is applicable only when neither the innovator product nor a reference country product is available or accessible, and must be justified in writing to the NMRA.

NOTE: *The applicant must document and justify the choice of comparator product in the application dossier. Supporting evidence such as the country of purchase, marketing authorisation details, batch number, expiry date, and assay content certificate must be provided.*

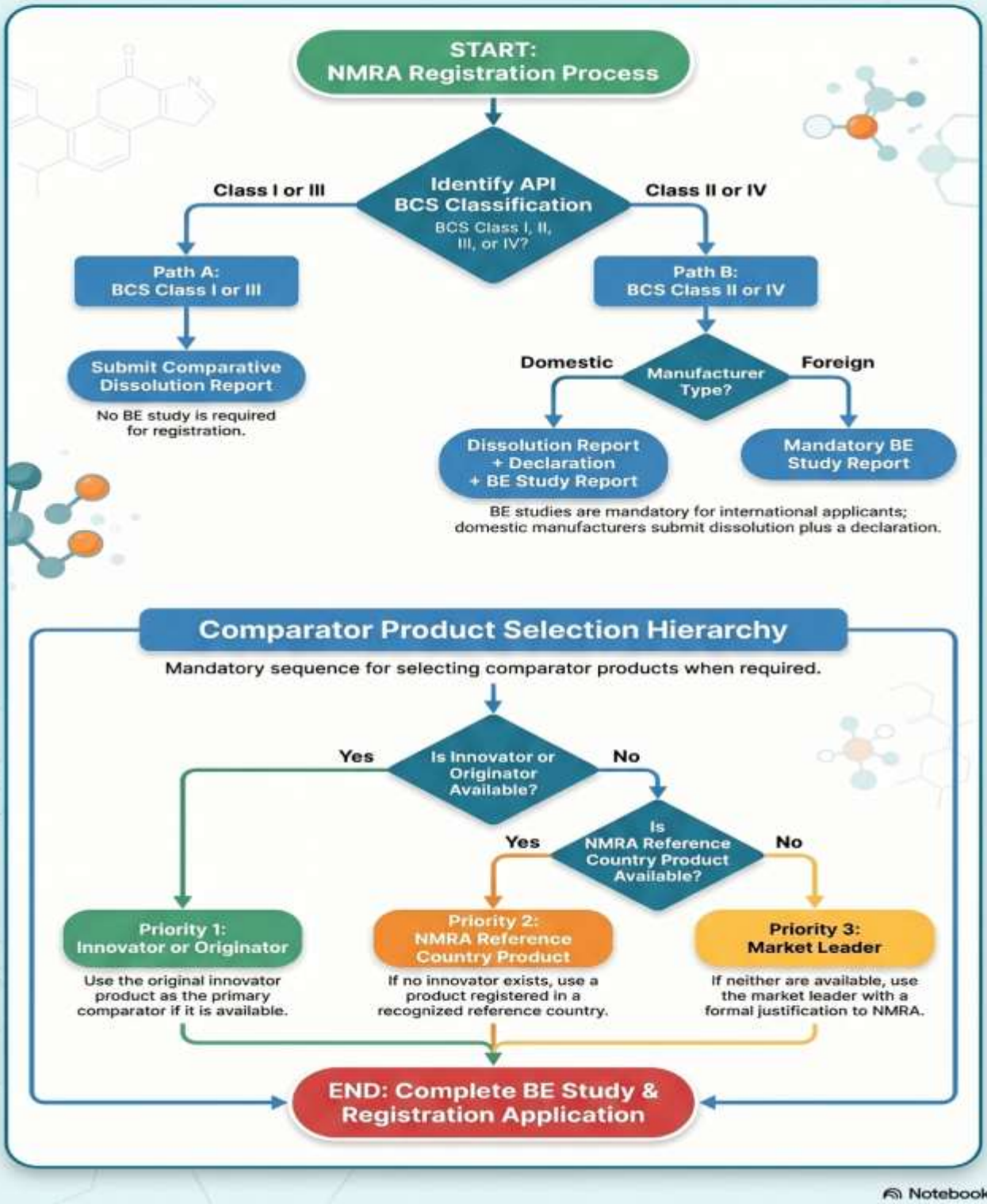
6.2. Comparator Product Selection Flow Chart

The following flowchart illustrates the decision process for selecting an appropriate comparator product:

Figure 1: Comparator Product Selection Flow Chart- NMRA, SL

NMRA Sri Lanka: Registration Pathway & Comparator Selection Flowchart

A step-by-step guide for pharmaceutical manufacturers to determine Bioequivalence (BE) study requirements and select appropriate comparator products for registration.



6.3. Requirements for the Comparator Product Batch

Regardless of the category of comparator selected, the following requirements apply to the comparator batch used in the BE study or CDR:

- The batch must be within its labelled shelf life at the time of the study/testing.
- A certificate of analysis (CoA) from the manufacturer must be provided.
- The assayed content of the comparator batch should not differ by more than 5% from that of the test product batch.
- The country of purchase and marketing authorization details must be documented.
- It is advisable to evaluate more than one batch of the comparator product and select the most representative batch.

6.4. Comparator Product Selection for Fixed-Dose Combination (FDC) Products

For FDC products, bioequivalence must be demonstrated for each active substance component of the combination independently. The failure to demonstrate BE for any single component of an FDC results in failure to demonstrate BE for the FDC product as a whole, and the application will not receive marketing authorization.

The selection of an appropriate comparator product for FDC BE studies is governed by the stepwise hierarchy set out in Section 6.4 of this guideline and is summarized below. Applicants must follow this hierarchy in the order presented and document their comparator selection rationale in the application dossier.

Comparator product selection for FDC products (in order of preference):

- Use the originator FDC product registered in Sri Lanka or an NMRA reference country (see Section 6.4.1). This is the preferred and simplest pathway.
- If the originator FDC is unavailable locally, import it from a Reference country identified by NMRA (see Section 6.4.2).
- If no originator FDC exists globally, use the individual originator single-ingredient products for each active substance as separate comparators and conduct component-specific BE studies (see Section 6.4.3).
- If individual originators are also unavailable, apply to the NMRA for prior written approval to use a scientifically justified foreign reference product (see Section 6.4.4).

Study design and bioanalytical requirements:

- BE studies for FDC products must use a pharmacokinetic sampling scheme suitable for the accurate determination of the PK parameters of all individual active components.

- Bioanalytical methods must be validated for the determination of each active substance in the presence of the other component(s) in the combination product. Cross-interference between components in the bioanalytical assay is not acceptable.
- PK parameters (AUC(0-t), AUC(0-inf), Cmax, tmax) must be reported separately for each active component. BE acceptance criteria (90% CI within 80.00-125.00%) apply independently to each component.
- For FDC products applied for multiple strengths, strength selection follows the dose-proportionality principles in Section 6.4.5, applied independently to each component.

> **NOTE:** *BCS-based biowaivers for FDC products may be considered only when ALL active substances in the combination belong to BCS Class I or III and all applicable excipient requirements are satisfied. If any single component does not satisfy the biowaiver criteria, an in vivo BE study is required for the entire FDC product.*

> **NOTE:** *The general comparator selection hierarchy established in Section 6.1 (Innovator/Originator first, Reference Country product second, Market Leader third) applies fully to FDC products. The additional guidance in this section addresses the specific stepwise approach applicable when the FDC originator product is unavailable or does not exist.*

6.4.1. Step 1: Use the Originator FDC Product (Preferred)

Where an originator FDC product exists and is registered in Sri Lanka or in an NMRA reference country, it must be used as the comparator product. This is the preferred pathway as it directly establishes therapeutic equivalence against the product that defined the clinical standard for the combination.

Where the originator FDC is registered in an NMRA reference country but not available on the Sri Lanka market, the applicant may import a batch of the originator FDC from the reference country for use as the comparator, subject to the batch documentation requirements set out in Section 6.3.

6.4.2. Step 2: Use a Reference Country Registered FDC (if Originator unavailable)

If the originator FDC is not available in Sri Lanka or in an NMRA reference country but a well-characterized reference FDC product is manufactured, authorized and available in another Reference country identified by the NMRA, that product may be imported and used as the comparator, subject to the following conditions:

- The product must be authorized by a recognized stringent regulatory authority (SRA).
- Evidence of quality comparability (assay content, dissolution profiles) must be provided.
- A scientific justification must be submitted to the NMRA confirming that the selected reference FDC represents the global therapeutic standard for the combination.

6.4.3. Step 3: Use Individual Originator Components (if No Originator FDC Exists)

In cases where no originator FDC product exists globally (e.g., for older drug combinations or locally developed FDCs), or where the originator FDC is not available in any Reference country, the individual originator (single-ingredient) products for each active substance in the combination must be used as comparators. In this scenario:

- A separate BE study or CDR must be conducted for each active component of the FDC, comparing each component against its individual originator reference product.
- Each BE study must use a bioanalytical method validated for the measurement of the relevant drug in the presence of the other component(s) of the FDC (see Section 9).
- The same test batch of the FDC product is used across all component-specific BE studies.
- Bioequivalence must be demonstrated for all individual active components. Failure to demonstrate BE for any single component constitutes failure to demonstrate BE for the FDC product as a whole.

6.4.4. Step 4: Use a Scientifically justified Foreign Reference Product

If neither an originator FDC nor individual originator single-ingredient products are available or accessible, the NMRA may permit the use of an alternative foreign reference product as the comparator, provided the applicant submits a comprehensive scientific justification to the NMRA prior to the study. This justification must include:

- Published literature evidence supporting the therapeutic equivalence and established use of the proposed reference product.
- Full regulatory approval history of the proposed reference product in its country of origin.
- Quality and pharmacokinetic comparability data demonstrating that the proposed reference product is representative of the global therapeutic standard for the combination.
- An explicit statement confirming that no originator FDC or individual originator components are available or accessible, with documentary evidence.

> **IMPORTANT:** *The use of a non-originator reference product for an FDC application requires prior written approval from the NMRA before the BE study or CDR is initiated. Applicants must submit a comparator justification data and obtain NMRA approval before proceeding. Studies conducted without prior approval may not be accepted.*

6.4.5. Strength Selection for FDC BE Studies

When an FDC product is applied for in multiple strengths, the selection of the strength(s) to be studied in vivo follows the same dose-proportionality principles as for single-ingredient products (see Section 7.5), applied independently to each active component of the FDC:

- Dose-proportional PK for all components: conduct the BE study at the highest strength.
- Greater than proportional increase in AUC or Cmax for any component: conduct at the highest strength.
- Less than proportional increase due to saturation of absorption: conduct at the lowest strength.
- Less than proportional increase due to limited solubility or unknown reasons: conduct BE studies at both the lowest and highest strengths.

> **NOTE:** *The strength selection criterion that is most conservative (requiring more extensive testing) across all active components governs the overall strength selection strategy for the FDC BE programme. BE must be demonstrated for each active component at each strength studied. A biowaiver for additional FDC strengths not studied in vivo may be considered if all components satisfy the general biowaiver criteria.*

6.4.6. Summary: Stepwise Comparator Selection for FDC products

Scenario	Comparator Selection	BE Requirement
Originator FDC registered in Sri Lanka or NMRA reference country	Use originator FDC product	BE demonstrated for each active component
Originator FDC available in ICH/WHO jurisdiction but not reference country	Import originator FDC from ICH/WHO jurisdiction with full documentation	BE demonstrated for each active component
No originator FDC exists globally	Use individual originator single-ingredient products for each component	Separate BE study per component; all must pass
No originator FDC or individual originators available	Scientifically justified foreign reference product (prior NMRA approval required)	BE demonstrated for each active component
Multiple FDC strengths applied for	Select strength(s) per dose-proportionality of each component; most conservative governs	BE for each active at each studied strength

7. DESIGN AND CONDUCT OF BIOEQUIVALANCE STUDIES

Bioequivalence studies submitted to the NMRA Sri Lanka must be designed and conducted in accordance with GL-021, ICH M13A, and applicable ICH guidelines on Good Clinical Practice (GCP). The following sections summarise the key requirements.

7.1. Study Design

The standard design for a bioequivalence study is a randomised, single-dose, two-period, two-sequence crossover study conducted in healthy volunteers. The treatment periods must be separated by a washout period of at least 5 terminal elimination half-lives (minimum 7 days) of the drug substance.

Alternative designs (parallel, replicate, multi-period) may be acceptable when scientifically justified, such as:

- Parallel design: For substances with very long elimination half-lives.
- Replicate design: For highly variable drug products (intra-subject CV > 30%).
- Multiple-dose design: When a single-dose study cannot be conducted for ethical or safety reasons.

7.2. Study Population

Studies should generally be conducted in healthy adult volunteers (aged 18 years and above, BMI 18.5–30.0 kg/m²). Patients may be used when the drug carries unacceptable safety risks in healthy volunteers. The minimum number of evaluable subjects is 12 for a crossover design, or 12 per treatment arm for a parallel design. Sample size calculations should be based on a priori power of at least 80% within the acceptance range of 80.00–125.00%.

7.3. Fasting and Fed Study Conditions

The study should generally be conducted under fasting conditions (at least 8 hours pre-dose fast), as this is most sensitive for detecting formulation differences. The following conditions apply:

Comparator Product Labelling / Product Type	Recommended Study Condition(s)
Labelled for fasting use or regardless of food	Single study under fasting conditions
Labelled for fed use (PK reasons)	Single study under fed conditions
Labelled for fed use (tolerability reasons only, non-high risk)	Fasting or fed conditions (either acceptable)
High-risk products (low solubility + complex formulation)	Both fasting AND fed studies required

In fed studies, the standard meal (for high-risk products) should be a high-fat (approximately 50% of total caloric content), high-calorie (approximately 900–1000 kcal) meal, consistent with ICH M13A recommendations.

7.4. Pharmacokinetic Parameters and Acceptance Criteria

The primary pharmacokinetic parameters for bioequivalence assessment are:

- AUC(0-t): Area under the plasma concentration-time curve from time zero to the last measurable concentration.
- Cmax: Maximum observed plasma concentration.
- AUC(0-72h) may be used instead of AUC(0-t) for drugs with long elimination half-lives (≥24 hours).

Bioequivalence is concluded when the 90% confidence interval (CI) for the geometric mean ratio (test/comparator) of each primary parameter lies within the acceptance range of 80.00–125.00%, using log-transformed data analysed by ANOVA.

Special Cases:

Narrow Therapeutic Index Drugs (NTIDs): Tightened acceptance criteria of 90.00–111.11% for AUC and, where clinically indicated, for Cmax. Highly Variable Drug Products (HVDPs): Widened Cmax acceptance range up to 69.84–143.19% may be applicable with replicate design and regulatory justification. AUC acceptance range remains 80.00–125.00%.

7.5. Strength to be Studied

The strength to be used in the BE study is determined by the dose proportionality of the drug's pharmacokinetics:

- Dose proportional PK (or greater than proportional increase in AUC/Cmax): Study at the highest strength.
- Less than proportional increase due to saturation of absorption: Study at the lowest strength.
- Less than proportional increase due to limited solubility or unknown reasons: Studies required at both the lowest and highest strengths.

A biowaiver for additional strengths (not studied in vivo) may be claimed if all general biowaiver criteria (proportional composition, same manufacturing process, and similar in vitro dissolution profiles) are satisfied.

8. COMPARATIVE DISSOLUTION REPORT (CDR) REQUIREMENST

A Comparative Dissolution Report (CDR) is required in the following situations:

1. As the primary submission for BCS Class I and Class III products (instead of an in vivo BE study).
2. As a provisional submission for domestic manufacturers of BCS Class II and Class IV products (accompanied by a Declaration Letter).
3. In support of a biowaiver for additional strengths not studied in vivo.

8.1. Dissolution Testing Requirements

Dissolution testing must be conducted at a minimum of three pH conditions to simulate physiological GI conditions:

- pH 1.2 (or 0.1 N HCl / Simulated Gastric Fluid without enzymes)
- pH 4.5 (acetate buffer)
- pH 6.8 (phosphate buffer / Simulated Intestinal Fluid without enzymes)

Standard apparatus and conditions:

Parameter	Specification
Apparatus	USP Apparatus I (Basket) or II (Paddle)
Volume	900 mL or less
Temperature	37 ± 1°C
Agitation (Paddle)	50 rpm (usual)
Agitation (Basket)	100 rpm (usual)
Sampling	At least every 15 min; e.g., 10, 15, 20, 30, 45 min
Number of units	12 units per experiment (for f2 evaluation)
Surfactants	Not acceptable for BCS-based biowaiver dissolution

8.2. Dissolution Profile Similarity Evaluation

Dissolution profile similarity between the test and comparator products must be demonstrated at each pH condition. The f2 similarity factor (Model-Independent method) is the standard approach:

f2 Similarity Factor:

An f2 value of 50–100 indicates that the two dissolution profiles are similar. Where more than 85% of drug is dissolved within 15 minutes for both products, profiles are considered similar without further mathematical evaluation. The f2 method requires at least 3 time points, not more than one mean value >85% dissolved, and coefficient of variation ≤20% at the first time point and ≤10% at subsequent time points.

8.3. Content of the Comparative Dissolution Report

The CDR submitted to the NMRA must include the following:

- Full description of the test and comparator product batches (batch number, batch size, manufacturing date, expiry date, assay content).

- Certificates of Analysis for both products.
- Justification for the choice of comparator product (see Section 6).
- Detailed description of dissolution test conditions (apparatus, media, agitation speed, temperature, volume, sampling schedule, analytical method).
- Individual and mean dissolution results at each pH condition, presented as tabular data and graphical profiles.
- Summary statistics (mean, SD, CV%) at each time point for each product and each pH.
- Similarity analysis (f2 calculation or alternative method) with interpretation.
- Bioanalytical method validation data (if applicable).
- Conclusions and assessment of biowaiver eligibility (where applicable).

9. BIOANALYTICAL REQUIREMENTS FOR BE STUDIES

The bioanalytical component of bioequivalence trials must be performed in accordance with the principles of Good Laboratory Practice (GLP) and ICH M10 (Bioanalytical Method Validation and Study Sample Analysis). The validated bioanalytical method must demonstrate adequate:

- Selectivity: The method must specifically measure the parent compound (or metabolite, where justified).
- Sensitivity: The lower limit of quantitation (LLOQ) should be at most 1/20th of Cmax, ensuring pre-dose concentrations can be detected at ≤5% of Cmax.
- Linearity (calibration curve performance).
- Accuracy and precision (within-run and between-run).
- Stability: Matrix, stock solution, freeze-thaw, and long-term stability must be documented.

In principle, bioequivalence must be based on the measurement of the parent compound. Measurement of a metabolite may only be used as a surrogate in exceptional cases where the parent compound cannot be reliably quantified (e.g., for certain inactive prodrugs), and must be specifically justified.

Reanalysis of study samples must follow pre-specified criteria documented in the study protocol or SOP. Samples must be analysed blinded to treatment assignment.

10. DATA ANALYSIS AND STATISTICAL REQUIREMENTS

10.1. Statistical Model

Pharmacokinetic parameters (AUC(0-t), Cmax, and other relevant parameters) must be log-transformed prior to analysis. The primary statistical analysis for crossover studies should use an Analysis of Variance (ANOVA) model with fixed effects for sequence, subject within sequence, period, and formulation. Non-parametric analyses are not acceptable.

Point estimates and 90% confidence intervals for the geometric mean ratio (test/comparator) must be presented for each primary PK parameter. The 90% CI must fall within the acceptance range of 80.00–125.00% for standard products (lower bound ≥80.00%, upper bound ≤125.00%, each rounded to two decimal places).

10.2. Subject Accountability and Exclusions

All treated subjects should be included in the statistical analysis. Exclusions from the analysis population must be pre-specified in the study protocol and documented before bioanalysis commences. Acceptable reasons for exclusion include protocol-specified events such as emesis within 2× median tmax, significant protocol deviations, or high pre-dose concentrations (>5% of Cmax in the relevant period). The minimum number of evaluable subjects is 12 (crossover). Exclusion of data on pharmacokinetic grounds alone is not acceptable.

10.3. Carry-Over Assessment

A formal carry-over test is not required. Carry-over potential should be assessed by examining pre-dose concentrations in Period 2 (and subsequent periods). Subjects with pre-dose concentrations >5% of their own Cmax in that period should be excluded from the statistical analysis for that period. In a two-period crossover, this results in exclusion of the subject from the entire analysis.

10.4. Two-Stage Adaptive Design

A two-stage adaptive design may be used. If adopted, appropriate alpha adjustment must be pre-specified in the study protocol to maintain the overall Type I error. For example, using 94.12% confidence intervals at both stages is an acceptable approach. A term for stage must be included in the ANOVA model for the combined analysis.

11. DOCUMENTATION AND STUDY REPORT REQUIREMENTS

The BE study report submitted to the NMRA must be comprehensive and include all documentation necessary to allow full evaluation and, if required, repetition of the pharmacokinetic and statistical analyses. The report must be written in accordance with ICH E3 (Structure and Content of Clinical Study Reports) and include:

- Study protocol (including any amendments).
- Names and affiliations of responsible investigator(s), study site(s), and execution period.
- Details of test and comparator products (name, strength, dosage form, batch number, assay content, manufacturer, expiry date, country of purchase of comparator product).
- Certificates of Analysis for both test and comparator batches.
- Individual plasma concentration-time data for all subjects (tabulated and graphical, linear and log-linear scale).
- Individual and summary pharmacokinetic parameters.

- Complete statistical analysis output (ANOVA tables, point estimates, 90% CI).
- Bioanalytical method validation report and study sample analysis report.
- List of all protocol deviations and subject exclusions with justification.
- Signed investigator statement.

12. SPECIAL CONSIDERATIONS

12.1. Narrow Therapeutic Index Drugs (NTIDs)

For products containing active substances classified as NTIDs, the NMRA will apply tightened bioequivalence acceptance criteria of 90.00–111.11% for AUC, and where clinically indicated for safety or efficacy, for Cmax as well.

12.2. Highly Variable Drug products (HVDPs)

For HVDPs (intra-subject CV >30% for Cmax), a replicate crossover study design should be used. A widened acceptance range for Cmax (up to 69.84–143.19%) may be considered using scaled average bioequivalence, provided the within-subject variability of the reference compound in the study exceeds 30% and the geometric mean ratio lies within 80.00–125.00%. The request for a widened interval must be prospectively specified in the study protocol. The AUC acceptance range remains at 80.00–125.00%.

12.3. Endogenous Compounds

For drug substances that are endogenous (naturally present in the body), baseline concentrations must be measured and appropriate baseline correction applied before pharmacokinetic analysis. The method of baseline correction must be pre-specified in the study protocol. Baseline correction should be period-specific. If baseline correction results in negative concentration values, these should be set to zero.

12.4. Fixed-Dose Combination (FDC) products

For FDC products, bioequivalence must be demonstrated for each active substance component. Failure to demonstrate BE for any single component results in failure to demonstrate BE for the FDC product as a whole. BE studies for FDC products should use a sampling scheme suitable for all components, with bioanalytical methods validated for each drug in the presence of the other component(s).

13. MODIFIED RELEASE (MR) DOSAGE FORMS- BIOEQUIVALENCE REQUIREMENTS

This section sets out the requirements of the NMRA Sri Lanka for the evaluation of bioequivalence of modified-release (MR) dosage forms. MR products are pharmaceutical forms

specifically designed to alter the rate, timing, or location of drug release compared to conventional immediate-release (IR) formulations. Because their therapeutic performance is intrinsically dependent on formulation design, a more extensive and rigorous set of bioequivalence studies is generally required compared with IR forms.

13.1. Scope and Classification of Modified Release Dosage Forms

Modified release dosage forms covered by this section include, but are not limited to:

- Extended-release (ER) / prolonged-release products - designed to release drug more slowly than conventional forms, reducing dosing frequency.
- Delayed-release products (e.g., enteric-coated tablets or capsules) - designed to release drug at a site other than the stomach.
- Multiphasic-release products- combining an immediate-release phase with one or more extended-release phases.
- Transdermal drug delivery systems (TDDS / patches) - designed to deliver drug through the skin at a controlled rate for systemic action.
- Modified-release pellets or multiparticulate systems - including capsules containing modified-release pellets or granules.

IMPORTANT: *Modified release dosage forms are NOT eligible for BCS-based biowaivers. In vivo bioequivalence studies are required for all MR products.*

13.2. General Principles for Bioequivalence Evaluation of MR Products

The general principles of bioequivalence set out in Sections 7 to 10 of this guideline apply equally to MR products. However, due to the formulation-dependent nature of drug release from MR dosage forms, additional studies and parameters are required to ensure that the test product performs equivalently to the reference product across the full range of physiological conditions likely to be encountered in clinical use.

The key additional considerations for MR products are:

- A single-dose fasting study alone is generally insufficient; food effect studies and, where applicable, steady-state studies are required.
- The risk of unintended rapid drug release (dose dumping) must be evaluated and excluded, both in vitro and, where necessary, in vivo.
- For TDDS, additional assessments of skin adhesion and local safety are required.

13.3. Standard Bioequivalence Study Designs for MR Products

The evaluation of bioequivalence for MR products generally requires a combination of studies to ensure comparable performance under the range of physiological conditions relevant to clinical use.

The following study designs are required or may be required depending on the product type and characteristics.

13.3.1. Single-Dose Fasting Study

A randomised, single-dose, crossover study in healthy volunteers under fasting conditions (at least 8 hours pre-dose fast) is the foundational bioequivalence study for all MR products. This study compares the test and reference products under conditions that provide maximum sensitivity for detecting formulation differences.

- Design: Two-period, two-sequence crossover (or replicate design, if indicated for highly variable products).
- Subjects: Minimum 12 evaluable healthy volunteers; sample size based on a priori power calculation (at least 80% power within 80.00-125.00% acceptance range).
- Washout: At least 5 terminal elimination half-lives between treatment periods.
- Fluid: 240 mL of water at room temperature administered with the dose (unless product-specific requirements differ).

13.3.2. Single-Dose Fed Study

A single-dose fed bioequivalence study is mandatory for all oral MR products. This study evaluates the impact of food on the relative performance of the test and reference products, which is particularly important for MR formulations whose release mechanism may be sensitive to changes in gastrointestinal (GI) conditions induced by food intake.

The standard meal for MR BE studies conducted under fed conditions is a high-fat, high-calorie meal:

- Total caloric content: approximately 800-1000 kcal.
- Fat content: approximately 50% of total caloric content (approximately 500-600 kcal from fat).
- Protein content: approximately 150 kcal from protein; carbohydrate content: approximately 250 kcal.
- Subjects should start the meal 30 minutes before dosing and complete it within 30 minutes.
- The meal composition (grams, kcal, and % caloric content for protein, carbohydrate, and fat) must be fully described in the protocol and study report.

> **NOTE:** *If the comparator product labelling specifies a particular meal type or food restriction, the meal used in the BE study should reflect that recommendation. Deviations must be scientifically justified in the study protocol.*

13.3.3. Multiple-Dose (Steady-State) Study

A multiple-dose steady-state bioequivalence study is required when there is a risk of drug accumulation that cannot be adequately assessed from single-dose data alone. A steady-state study is specifically required if:

- The mean AUC(0-tau) after the first dose covers less than 90% of the mean AUC(0-inf), indicating significant drug accumulation with repeat dosing; OR
- The drug exhibits nonlinear pharmacokinetics across the therapeutic dose range; OR
- The product labelling or clinical use is exclusively for chronic (long-term) administration; OR
- Single-dose studies cannot be conducted in healthy volunteers for safety or tolerability reasons and the study must be conducted in patients.

In steady-state studies, the washout period of the previous treatment may overlap with the build-up phase of the second treatment, provided the build-up period is sufficiently long (at least 5 terminal elimination half-lives). The attainment of steady state must be confirmed by demonstrating stable pre-dose trough concentrations over at least 3 consecutive dosing intervals prior to the pharmacokinetic sampling day.

13.4. Pharmacokinetic Parameters to be Analysed

The pharmacokinetic parameters required for bioequivalence assessment depend on the study design (single-dose or multiple-dose) and the type of MR product. All parameters must be derived using non-compartmental methods from actual (not nominal) sampling times.

Study Type / Product Type	Primary PK Parameters (BE assessment)	Additional Parameters (study validity)
Single-Dose Studies (Fasting and Fed)	AUC(0-t), AUC(0-inf), Cmax	tmax, t1/2, residual area; AUC(0-t) should cover at least 80% of AUC(0-inf)
Multiple-Dose / Steady-State Studies	AUC(0-tau), Cmax,ss, Ctau,ss (trough concentration at end of dosing interval)	tmax,ss, fluctuation index [(Cmax,ss - Cmin,ss)/Cavg,ss], swing [(Cmax,ss - Cmin,ss)/Cmin,ss]
Multiphasic / Biphasic Products	AUC(0-t), AUC(0-inf), Cmax (overall); partial AUC and Cmax for each distinct release phase	tmax for each phase; shape of overall concentration-time profile
Delayed-Release Products	AUC(0-t), AUC(0-inf), Cmax	tmax, tlag (lag time to onset of absorption); no apparent difference in median tmax acceptable

NOTE: *For products with very long elimination half-lives (24 hours or longer), AUC(0-72h) may be used as a surrogate for AUC(0-t) in single-dose studies, as it adequately captures the absorption phase of MR products. The AUC(0-t) should cover at least 80% of AUC(0-inf).*

13.5. Bioequivalence Acceptance Criteria for MR Products

The standard bioequivalence acceptance criteria apply to MR products as follows:

Parameter	Acceptance Criterion	Applicable Study Type
AUC(0-t), AUC(0-inf), AUC(0-tau)	90% CI of geometric mean ratio (test/reference) within 80.00-125.00%	Single-dose and steady-state studies
Cmax (single dose) and Cmax,ss (steady state)	90% CI of geometric mean ratio (test/reference) within 80.00-125.00%	All study designs
Ctau,ss (trough at steady state)	90% CI within 80.00-125.00%	Multiple-dose studies only
tmax and tmax,ss	No apparent difference in median tmax and its variability between test and reference	All designs (no formal statistical test required)
Partial AUC (pAUC)	90% CI within 80.00-125.00% for the pre-specified clinically relevant time window	Multiphasic products and early-exposure relevant products
NTIDs: AUC and Cmax where applicable	Tightened criteria: 90% CI within 90.00-111.11%	All designs for narrow therapeutic index drugs

For delayed-release and multiphasic formulations, in addition to meeting the quantitative acceptance criteria above, there must be no apparent difference in the median tmax and its variability between the test and reference products. A marked difference in tmax may indicate a difference in release pattern that is clinically unacceptable even if the AUC and Cmax confidence intervals fall within the acceptance range.

13.6. Required Pharmaceuticals, Formulations and In Vitro Data

Applications for registration of MR dosage forms must be supported by comprehensive pharmaceutical and formulation data that justify the design of the modified-release mechanism and demonstrate its robustness. The following data are required as part of the submission dossier.

13.6.1. Release Mechanism Justification

A complete scientific justification of the release-controlling mechanism must be provided. This should include:

- Description of the release-controlling component (e.g., polymer matrix, membrane coat, osmotic system, lipid-based system, ion-exchange resin, multiparticulate architecture).
- Explanation of how the release rate is controlled and why the design is appropriate for the drug substance and the intended clinical indication and dosing regimen.
- Discussion of the sensitivity of the release mechanism to physiological variables such as pH, GI motility, food intake, and GI transit time.

13.6.2. Comparative In Vitro Dissolution Profiles

Comparative in vitro dissolution profiles must be provided for test and reference product batches across a range of conditions:

- Multiple pH values: pH 1.2, 4.5, and 6.8 (phosphate or acetate buffers), and where relevant pH 6.0 and pH 7.5 for enteric-coated and colonic delivery systems.
- Multiple time points sufficient to characterise the full release profile over the intended dosing interval (e.g., for a 24-hour ER product, sampling at appropriate intervals up to 24 hours).
- Apparatus: USP Apparatus I (basket) at 100 rpm or USP Apparatus II (paddle) at 50 rpm, or an appropriately justified alternative (e.g., flow-through cell).
- Minimum 12 units per test condition; individual and mean results with summary statistics (mean, SD, CV%) must be presented graphically and in tabular form.

> **NOTE:** *For MR products, the f2 similarity factor is applicable only when less than 85% of drug has dissolved at the first time point and dissolution is not complete within 15 minutes. Given the extended release profile of MR products, only one time point may exceed 85% dissolved when applying the f2 test. Alternative statistical approaches (e.g., model-dependent methods, ANOVA-based multivariate comparison) may be acceptable if pre-specified and justified.*

13.6.3. Alcohol-Induced Dose Dumping Studies

In vitro studies evaluating the effect of ethanol on drug release are mandatory for all oral MR solid dosage forms. These studies are required to exclude the risk of alcohol-induced dose dumping, defined as the unintended, rapid release of the entire or a large fraction of the drug dose when the product is co-ingested with alcoholic beverages.

Alcohol interaction studies must be conducted as follows:

- Dissolution testing in dissolution media containing ethanol at concentrations of 0%, 5%, 20%, and 40% v/v (in addition to standard aqueous media at each relevant pH).
- Any significant increase in drug release rate (e.g., more than 20% increase in drug released at any time point compared with the standard aqueous medium) must be reported, and a risk assessment of clinical significance provided.
- If a clinically significant risk of dose dumping is identified from in vitro data, an in vivo study evaluating the pharmacokinetic profile of the product co-administered with a moderate dose of ethanol may be required by the NMRA.

IMPORTANT: *A demonstrated risk of significant alcohol-induced dose dumping in vitro will require mitigation by product label warning and/or reformulation.*

14. GLOSSARY OF KEY TERMS

Term	Definition
Bioavailability (BA)	The rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form and becomes available at the site of action.
Bioequivalence (BE)	Two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) lie within acceptable predefined limits after administration in the same molar dose.
BCS Class I	Drug substance with high solubility AND high permeability.
BCS Class II	Drug substance with low solubility and high permeability. Absorption is dissolution rate-limited.
BCS Class III	Drug substance with high solubility and low permeability.
BCS Class IV	Drug substance with low solubility AND low permeability. Poor oral bioavailability.
Comparator Product	The drug product accepted by the NMRA against which the test product is compared in a BE study or comparative dissolution study.
Comparative Dissolution Report (CDR)	A report presenting in vitro dissolution profile similarity data comparing test and comparator products, submitted in lieu of or complementary to an in vivo BE study.
Declaration Letter	A formal commitment letter submitted by a domestic manufacturer stating intent and timeline for submission of a full BE study report.
Domestic Manufacturer	A pharmaceutical manufacturer whose manufacturing facility is located within Sri Lanka.
f2 (Similarity Factor)	A model-independent mathematical index used to compare dissolution profiles; values between 50 and 100 indicate similarity.
Highly Variable Drug Product (HVDP)	A drug product for which intra-subject variability for a PK parameter (typically Cmax) exceeds 30%.
Innovator/Originator Product	The first product to be authorised based on a full quality, safety, and efficacy dossier.
Market Leader	The pharmaceutical product with the highest sales volume or market share in Sri Lanka for the same active substance and dosage form.
NMRA	National Medicines Regulatory Authority, Sri Lanka.
Narrow Therapeutic	A drug where small differences in dose or blood concentration may

Term	Definition
Index Drug (NTID)	lead to serious therapeutic failures or adverse reactions.
Pharmaceutical Equivalence	Products containing the same amount of the same active substance in the same dosage form meeting the same or comparable standards.
Reference Country	A country identified by the NMRA as having a rigorous medicine regulatory system, whose registered products may serve as comparators.
Test Product	The product for which marketing authorisation is sought, compared against the comparator in a BE study or CDR.

15. REFERENCES

- European Medicines Agency (EMA). Guideline on the Investigation of Bioequivalence. CPMP/EWP/QWP/1401/98 Rev. 1/Corr **. January 2010.
- ICH M13A Guideline on Bioequivalence for Immediate-Release Solid Oral Dosage Forms. Step 5. Final adoption by CHMP 25 July 2024.
- ICH M13A Questions and Answers. EMA/CHMP/ICH/325575/2024. 25 July 2024.
- ICH M9 Guideline: Biopharmaceutics Classification System-Based Biowaivers.
- ICH M10 Guideline: Bioanalytical Method Validation and Study Sample Analysis.
- ICH E6 (R2): Good Clinical Practice.
- ICH E3: Structure and Content of Clinical Study Reports.
- WHO Technical Report Series: Multisource (Generic) Pharmaceutical Products. Guidelines on Registration Requirements to Establish Interchangeability.
- National Medicines Regulatory Authority. (2024). Guidelines on registration of medicines (GL-021).

16. APPENDIX A- TEMPLATE DECLARATION LETTER

[Company Letterhead]

Date: _____

The Chief Executive Officer
National Medicines Regulatory Authority
Sri Lanka

Dear Sir,

DECLARATION OF COMMITMENT TO SUBMIT BIOEQUIVALENCE STUDY REPORT

We, [Company Name], a pharmaceutical manufacturer with manufacturing facilities located in Sri Lanka [Address], hereby submit this Declaration Letter in respect of the following product for which a Marketing Authorisation Application has been filed with the NMRA:

Product Name:	[Product Name]
Active Pharmaceutical Ingredient:	[INN]

Strength(s):	[Strength(s)]
Dosage Form:	[e.g., Film-coated Tablet]
BCS Classification:	[Class II / Class IV]
Application Reference Number:	[NMRA Ref. No.]

We hereby confirm and declare that:

1. We have submitted a Comparative Dissolution Report (CDR) as part of our Marketing Authorisation Application for the above product, in accordance with the NMRA Guideline on the Review of Bioequivalence (GL-xxx).
2. We commit to conducting a full in vivo bioequivalence study for the above product in accordance with NMRA GL-021, this supplementary guideline, and applicable ICH guidelines.
3. We commit to submitting the full bioequivalence study report to the NMRA within [specify: e.g., 24/36 months] from the date of grant of provisional registration.
4. We understand and accept that full registration will not be granted until an acceptable bioequivalence study report demonstrating bioequivalence between our product and the selected comparator has been submitted and approved by the NMRA.
5. We accept that the NMRA reserves the right to withdraw provisional registration if the bioequivalence study report is not submitted within the committed timeline, or if the submitted study fails to demonstrate bioequivalence.
6. The bioequivalence study will be conducted using a batch that is representative of the to-be-marketed product, using the following comparator product: [Comparator name, strength, batch number, country of purchase].

We make this declaration in good faith and confirm the accuracy and completeness of the information provided.

Signed: _____

Name: _____

Designation: _____

Company Name: _____

Date: _____

Company Seal: _____

17. FEEDBACK

13.1 Staff and customers may provide feedback about this document by emailing, info@nmra.gov.lk.

18. CHANGE HISTORY

Revision No	Effective Date	Description of change(s)	Section(s) modified
		Initial Publication	Initial Publication

19. APPROVAL AND REVIEW DETAILS

	NAME	SIGNATURE
Prepared by		

Reviewed By		
Recommended By		
Approved by		

Next Review Date	