



Regulatory Divergence in Narrow Therapeutic Index Drugs: A Comparative Review of the US, EU, Japan, Canada, and South Korea

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Abstract

Generic drugs offer cost-effective alternatives to brand-name medications while ensuring comparable safety and efficacy. However, narrow therapeutic index drugs (NTIDs), which require precise dosing due to narrow margins between therapeutic and toxic concentrations, present additional regulatory challenges. Concerns regarding the interchangeability of generic NTIDs are amplified by international variation in definitions, bioequivalence (BE) standards, and regulatory approaches. This systematic review compares NTID-related regulatory frameworks across major authorities to inform the development of the ICH M13C guideline and foster global harmonization of evaluation standards for generic NTIDs. A comprehensive comparative analysis was conducted of NTID-related regulatory frameworks in five ICH member countries (United States [US], European Union [EU], Japan, Canada, and South Korea), with Egypt, Jordan, and Saudi Arabia included as reference countries. Data were obtained from literature searches and official regulatory sources, focusing on NTID definitions, BE standards, and NTID lists. Marked regulatory divergence was observed. South Korea uniquely incorporates quantitative pharmacological and toxicological criteria into NTID definitions. The US employs the most stringent NTID BE standards, utilizing a fully replicated design, reference-scaled average bioequivalence (RSABE), and variability assessment. Only cyclosporine and tacrolimus are classified as NTIDs by all five core countries. Variability in NTID lists and evaluation criteria complicates global harmonization efforts. Achieving consistent evaluation and safe international use of generic NTIDs requires global alignment on definitions, BE criteria, and NTID lists. This review supports integrating real-world data into regulatory decision-making and advances the ICH M13C guideline.

Keywords Bioequivalence · Generic drugs · ICH M13C guideline · Narrow therapeutic index · Regulatory harmonization

Introduction

Generic drugs provide equivalent quality, safety, and efficacy to original drugs while generally being more affordable (1, 2). These attributes allow generic drugs to substantially lower healthcare costs, enhance patient access to treatment, and support the stability of public healthcare insurance systems. The development of cost-effective generic drugs with scientifically demonstrated safety and efficacy is especially critical in treatment contexts requiring long-term medication for chronic or severe diseases (3). With the accelerating trend of population aging, many countries are implementing policies to promote the use of generics as part of strategies to sustain healthcare funding. In this context, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) initiated work on the “M13: Bioequivalence for Immediate-Release Solid Oral Dosage Forms” guideline in November 2019. The

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ICH continues to develop the M13 guideline series, which provides comprehensive guidance on bioequivalence (BE) studies. Despite this progress, persistent perceptions remain that generic drugs may be inferior to original drugs regarding safety and efficacy. Such concerns are particularly acute for drugs with narrow therapeutic index (NTI), in which minor differences in dosage or plasma concentration may result in therapeutic failure or serious adverse events (4, 5). This necessitates more precise and scientifically robust regulatory oversight. For reference, although some regulatory agencies use varying terms to refer to these drugs—such as “NTI drugs”, “narrow therapeutic index drugs” (NTIDs), and “narrow therapeutic range drugs” (NTRDs)—further examination of major biomedical databases—including International Pharmaceutical Abstracts (IPA), Medline, and Toxline—demonstrates that “narrow therapeutic index drug” and “narrow therapeutic index” are the most widely used and recognized terms (6). Accordingly, this review adopts the abbreviation “NTID”, reflecting the term with the greatest prevalence in the literature. Representative NTIDs, including warfarin (anticoagulant), phenytoin (antiepileptic), and tacrolimus (immunosuppressant) among others, are often prescribed long-term to patients with chronic or severe illnesses. Accordingly, establishing systematic and reliable standards to ensure the quality, safety, and efficacy of NTIDs is imperative. Such standards are essential for fostering confidence that generic NTIDs deliver therapeutic outcomes equivalent to those of original NTIDs.

However, significant discrepancies exist among regulatory authorities regarding NTID terminology, definitions, BE evaluation criteria, and NTID lists. These inconsistencies impede international harmonization and delay the global development of generic pharmaceuticals. Such variation in BE criteria may prompt some regulatory agencies to reject foreign clinical data that do not comply with their local standards, resulting in additional BE studies and increased development timelines and costs for pharmaceutical companies (5). Although cross-border mechanisms such as WHO Prequalification (WHO PQ) recognition (7) and the ASEAN Joint Assessment and Mutual Recognition Arrangements (MRAs) (8) facilitate acceptance of foreign BE data, high-risk drugs like NTIDs are frequently excluded. In these cases, regulatory authorities may require supplementary clinical data on safety and efficacy beyond standard BE studies.

To address these challenges, the ICH began discussions in February 2025 on the M13C guideline, which focuses on the design and evaluation of complex BE studies, including those for NTIDs. This guideline is scheduled for official adoption (Step 4) in February 2029. The ICH initiative highlights the importance of developing generic drugs according to harmonized global standards. Accordingly, to inform the ongoing development of the ICH M13C guideline, a

precise comparison and analysis of country-specific regulatory approaches to NTIDs is needed. Identifying whether regulatory standards are stricter or more permissive, and understanding the rationale for these differences, can inform the formulation of an international guideline for regulatory authorities worldwide. Such analysis will improve consistency and transparency in the global development and regulatory review of generic NTIDs, ultimately supporting the shared goal of optimizing patient safety through evidence-based regulatory practices.

Previous research on NTID BE includes the work of Gozzo *et al.*, who investigated the bio-creep phenomenon in generic drugs, a process whereby therapeutic efficacy may gradually decline when multiple generics are sequentially approved on the basis of prior bioequivalence studies (9). In addition, Donnelly *et al.* and Anno *et al.* examined the BE evaluation system for NTIDs in the US (10, 11). However, Gozzo *et al.* provided only a brief comparison of NTID BE criteria across countries. Although Donnelly *et al.* and Anno *et al.* compared terminology, definitions, BE evaluation criteria, and NTID lists between countries, their analyses primarily focused on the US and did not comprehensively address international regulatory systems or inter-country variation in the management of generic NTIDs. Therefore, this review aims to systematically compare and analyze NTID-related regulatory frameworks—including terminology and definitions, BE evaluation criteria, and NTID lists—across major regulatory agencies. This analysis will serve as a valuable resource for the development of the ICH M13C guideline and support the establishment of a robust evaluation system for generic NTIDs based on scientific evidence. Ultimately, the objective is to provide actionable guidance for stakeholders in the global generic pharmaceutical sector, including multinational pharmaceutical companies, generic drug developers, and regulatory authorities, thereby facilitating the efficient development and distribution of harmonized generic NTIDs with assured safety and efficacy.

Methods

This review proposes regulatory improvements to enhance the safety and efficacy of generic NTIDs by conducting a comparative analysis of country-specific NTID regulatory approaches. Five countries were selected as the primary subjects of analysis: the US, EU, Japan, Canada, and South Korea. Selection was based on regulatory influence within ICH membership and the availability of relevant data (12). Additionally, Egypt, Jordan, and Saudi Arabia—all of which publicly provide NTID lists through their regulatory agencies—were included as reference countries. Brief information from these countries is provided in supplemental 1. The rationale for selecting these jurisdictions reflects the current

regulatory landscape, where NTID-related elements such as terminology, definitions, and BE criteria vary internationally. Understanding these differences among countries that disclose NTID information is expected to support global generic NTID development and regulatory review, and inform the development of international guidelines.

Data collection employed a combination of keyword-based searches and snowballing methods. Relevant studies on NTIDs published in domestic and international journals were identified using databases such as PubMed, the Korean Citation Index (KCI), and Google Scholar. Key search terms included “generic drug,” “narrow therapeutic index drug,” “narrow therapeutic range drug,” “critical dose drug,” and “bioequivalence.” Additional literature was identified via backward snowballing, which entailed reviewing the reference lists of initially selected articles, and via forward snowballing, which involved identifying subsequent publications that cited the already-identified references, to locate further pertinent materials related to NTIDs and BE. To analyze the current regulatory status of NTIDs worldwide, the official websites of the regulatory authorities in the US, EU, Japan, Canada, South Korea, Egypt, Jordan, and Saudi Arabia were reviewed as of March 1, 2025. Regulatory documents, guidelines, and other published materials were examined to compare NTID-related terminology, definitions, BE evaluation criteria, and NTID lists. Approval status and NTID designation for specific drugs were verified using national drug approval databases and pharmaceutical information systems. Based on the collected data, this review analyzed differences in regulatory frameworks for generic NTIDs across countries and examined international efforts—including those of the ICH—regarding NTID-related issues. The ultimate aim was to propose improvements to the regulatory and evaluation systems for generic NTIDs. The official websites of the regulatory authorities from each country included in the analysis are provided in supplemental 1.

Results

Comparison of NTID Terminology and Definitions by Country

Currently, there is no clear consensus regarding the terminology, definition, or defining features of NTIDs. Terms including narrow therapeutic index, narrow therapeutic window, narrow therapeutic range, and narrow therapeutic ratio are often used interchangeably. However, these expressions differ in meaning, and careful selection of terminology is warranted because, from a linguistic perspective, only “window” or “range” appropriately convey the idea of width, whereas “index” and “ratio” do not inherently describe magnitude (6).

Review of terms used by national regulatory agencies indicates that the US most frequently uses “NTI drug,” EU uses “NTID,” Japan uses “NTRD,” Canada uses “CDD” (critical dose drug), and South Korea employs “active substance with a narrow therapeutic index.”

Definitions of NTIDs also vary among countries. The US, Canada, and South Korea provide explicit definitions through regulatory frameworks or guidelines, whereas the EU and Japan do not offer official definitions. Comparison of definitions from the US, Canada, and South Korea reveals minor differences in wording and criteria, but all describe NTIDs as drugs for which small changes in dose or blood concentration may result in serious therapeutic failure or significant adverse effects. Notably, South Korea specifies quantitative pharmacological and toxicological criteria, further defining NTIDs as drugs for which “the median lethal dose (LD_{50}) is less than twice the median effective dose (ED_{50}), or the minimum toxic concentration (MTC) is less than twice the minimum effective concentration (MEC) (13).” A similar criterion appears in the US Code of Federal Regulations (21 CFR 320.33(c)), but it is presented as an example of evidence for a narrow therapeutic ratio rather than as an official NTID definition (14). Table 1 summarizes NTID terminology and definitions across the five target countries.

Comparison of BE Evaluation Criteria for Generic NTIDs by Country

All five countries analyzed in this review use the same primary pharmacokinetic parameters to assess BE in generic drug studies: AUC_t (area under the plasma concentration–time curve), representing the extent of drug absorption, and C_{max} (maximum plasma concentration), reflecting the drug’s peak plasma concentration. Acceptance ranges for AUC_t and C_{max} are defined as the 90% confidence intervals (CIs) of the geometric mean ratios (GMRs) between test and reference products, calculated after log-transformation and statistical analysis of the respective AUC_t and C_{max} values. BE is determined by whether these CIs fall within the specified acceptance ranges. For generic drugs, all five countries adopt the internationally accepted BE range of 80.00–125.00% for both AUC_t and C_{max} . This standard demonstrates that the generic product’s pharmacokinetic profile is sufficiently similar to that of the original drug (25).

For generic NTIDs, stricter BE evaluation criteria are applied because even minor changes in plasma concentration can markedly affect safety and efficacy. Examination of BE evaluation standards for generic NTIDs across the five countries revealed significant differences in specific criteria. In the EU, the acceptance range for AUC_t in generic NTIDs is narrowed to 90.00–111.11%, while the range for C_{max} remains at 80.00–125.00%, as with generics. However,

Table I Terminology and Definitions of NTIDs by Country

Regulatory Agency	Terminology	Definition
US FDA (15)	NTI drug	Drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity
EU EMA ^a	NTID	NA
Japan PMDA ^a	NTRD	NA
Canada Health Canada (16)	CDD	Drugs where comparatively small differences in dose or concentration lead to dose- and concentration-dependent serious therapeutic failures and/or serious adverse drug reactions which may be persistent, irreversible, slowly reversible, or life threatening, which could result in inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or death
South Korea MFDS (13)	Active substance with a narrow therapeutic index	Active substances classified under [Appendix 1], or those with LD ₅₀ less than twice ED ₅₀ , or MTC less than twice MEC, or substances for which minor changes in dose or concentration are likely to cause relatively severe therapeutic failure or adverse effects compared to other drugs

CDD critical dose drug, ED₅₀ effective dose for 50% of the population, EMA European Medicines Agency, FDA Food and Drug Administration, LD₅₀ lethal dose for 50% of the population, MEC minimum effective concentration, MFDS Ministry of Food and Drug Safety, MTC minimum toxic concentration, NA not available, NTID narrow therapeutic index drug, NTRD narrow therapeutic range drug, PMDA Pharmaceuticals and Medical Devices Agency

^aDefinition of NTID is provided in the ICH M9 Guideline on Biopharmaceutics Classification System-based Biowaivers – Questions and Answers. Since EMA and PMDA do not provide their own definitions of NTIDs, these entries are indicated as NA

if $C_{\max}$ is deemed critical for safety, efficacy, or therapeutic drug monitoring (TDM), the stricter 90.00–111.11% range is also applied to $C_{\max}$. Japan maintains the standard range of 80.00–125.00% for both AUC_t and $C_{\max}$ when evaluating generic NTIDs. However, if the study includes at least 20 subjects (10 per group) and dissolution testing demonstrates similarity between the generic and reference products under all conditions, the stricter acceptance range of 90.00–111.11% may be applied to both AUC_t and $C_{\max}$. Canada sets the acceptance range for AUC_t at 90.00–112.00%, while retaining the 80.00–125.00% range for $C_{\max}$. South Korea adopts criteria similar to those of the EU, applying a 90.00–111.11% range for AUC_t and maintaining 80.00–125.00% for $C_{\max}$.

Unlike the other countries, the US employs a distinct approach to evaluating BE for generic NTIDs. Whereas most countries use a standard two-way crossover design, the US requires a fully replicated four-way crossover design for these evaluations. In the two-way crossover design, participants are divided into two groups, and each group receives both the test and reference products in a crossover manner. Each subject receives both formulations once. This design is commonly used for generic drug evaluation due to its simplicity and cost efficiency, and it minimizes inter-subject variability by allowing each participant to serve as their own control. However, this approach is limited in estimating within-subject variability, as repeated administration of the same formulation to the same individual is necessary for such estimation. In contrast, the fully replicated four-way crossover design requires each participant to receive both the test and reference formulations twice, enabling more

accurate estimation of within-subject variability. Given the narrow therapeutic index of NTIDs, the US mandates this design to achieve a more precise and reliable BE evaluation (10). Schematic diagrams of the two-way and fully replicated four-way crossover designs for generic NTID BE studies are presented in Fig. 1.

Additionally, the US requires that both mean comparison and variability comparison criteria be met for BE evaluation of generic NTIDs (1). Mean comparison assesses whether the generic drug produces, on average, an equivalent effect to the reference product, typically by determining whether the 90% CIs for AUC_t and $C_{\max}$ fall within the standard BE range of 80.00–125.00%. The FDA, however, employs a more sophisticated approach by incorporating Reference-Scaled Average Bioequivalence (RSABE) criteria. RSABE scales the BE limits based on the within-subject variability of the reference product, enabling a more precise mean comparison. Thus, in the US, generic NTIDs must meet both the reference-scaled limits calculated using RSABE and the conventional unscaled average BE limits. Variability comparison evaluates whether the consistency of the generic drug's effect—that is, the stability of its efficacy across individuals—is equivalent to that of the reference product. This assessment requires a replicate study design. The FDA applies a specific requirement: the upper bound of the 90% CI for the ratio of within-subject standard deviations between test and reference products (SWT/SWR) must not exceed 2.5. This criterion reflects the FDA's position that a generic product with pharmacokinetic variability more than 2.5 times that of the original cannot be considered equivalent. Therefore, US BE standards for generic NTIDs are

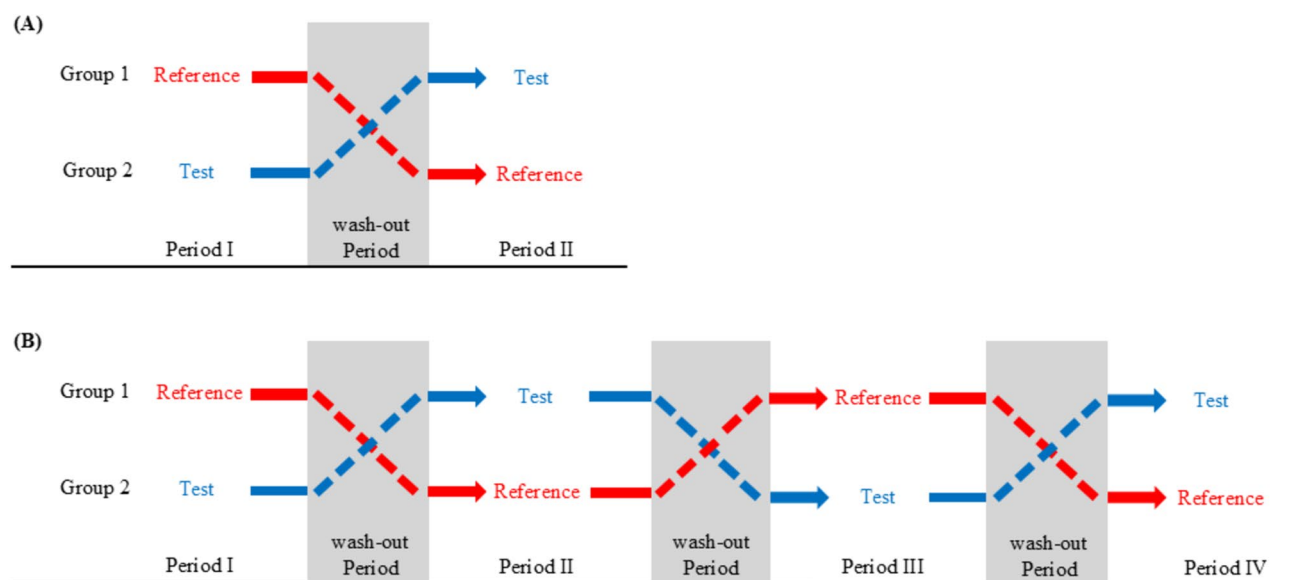


Fig. 1 BE Study Designs for Generic NTIDs by Country: Two-way Crossover Design in the EU, Japan, Canada, and South Korea **(A)** and Fully Replicated Four-way Crossover Design in the US **(B)**

structured to confirm both the average therapeutic effect and the consistency of that effect. This more rigorous standard aims to maximize patient safety and therapeutic reliability. A comparison of BE evaluation criteria for generic NTIDs across the five countries is provided in Table II.

Comparison of NTID Lists by Country

Based on Donnelly *et al.* (10), which compared NTID lists across countries, a comparative analysis was conducted on

the 38 substances classified as NTIDs in the five target countries. As of March 1, 2025, the approval status and NTID designation for each substance were verified using the websites and drug information systems of the respective national regulatory agencies. Table III summarizes these results. For the US, information on substance-specific approval status and NTID designation was obtained from the FDA's Orange Book and the Product-Specific Guidances (PSGs). Because the FDA does not maintain a separate NTID list but instead includes NTID designation information within the PSGs,

Table II Criteria for Bioequivalence Evaluation of Generic NTIDs by Country

Regulatory agency		US FDA (18)	EU EMA (19, 20)	Japan PMDA (21, 22)	Canada Health Canada (16, 23)	South Korea MFDS (13, 24)
PK parameters		AUC_t^a , C_{max}^a				
Generic drugs	BE acceptance range	80.00–125.00%				
	BE study design	Fully replicated 4-way crossover				
Generic NTIDs	BE acceptance range	AUC_t^a	1) Unscaled BE limits 2) RSABE limits 3) 90% CI upper bound of SWT/ SWR ≤ 2.5	90.00–111.11% 80.00–125.00% (90.00–111.11% if required)	2-way crossover (90.00–111.11% if required)	90.00–112.00% 80.00–125.00% 80.00–111.11% 80.00–125.00%
		C_{max}^a				

AUC_t area under the plasma concentration–time curve, *BE* bioequivalence, *CI* confidence interval, C_{max} maximum plasma concentration, *EMA* European Medicines Agency, *FDA* Food and Drug Administration, *MFDS* Ministry of Food and Drug Safety, *PK* pharmacokinetic, *PMDA* Pharmaceuticals and Medical Devices Agency, *RSABE* reference-scaled average bioequivalence

^aThe 90% CI of the geometric mean ratio (GMR) between the test and reference products for the evaluation parameter, calculated following log-transformation and statistical analysis

Table III Active Substances Designated as NTIDs by Country

Regulatory Agency	US FDA	EU EMA	Japan PMDA (26)	Canada Health Canada (16)	South Korea MFDS (13)
Acenocoumarol	-	NTID	-	-	-
Aprindine	-	-	NTRD	-	NTID
Carbamazepine	NTID		NTRD		NTID
Clindamycin			NTRD		NTID
Clonazepam			NTRD		NTID
Clonidine			NTRD		NTID
Colchicine		NTID			
Cyclosporine	NTID		NTRD	CDD	NTID
Digitoxin	-		NTRD	-	NTID
Digoxin	NTID		NTRD	CDD	NTID
Disopyramide			NTRD		NTID
Ethinyl estradiol			NTRD		NTID
Ethosuximide			NTRD		NTID
Everolimus	NTID	NTID			NTID
Flecainide				CDD	NTID
Glybuzole	-	-	NTRD	-	-
Guanethidine	-	-	NTRD	-	NTID
Isoetharine	-	-	-	-	NTID
Isoprenaline (isoproterenol)			NTRD		NTID
Levothyroxine	NTID	NTID			NTID
Liothyronine	NTID		-		NTID
Lithium	NTID		NTRD	CDD	NTID
Metaproterenol (orcioprenaline)		-	-		NTID
Methotrexate			NTRD		NTID
Minoxidil			-		NTID
Phenobarbital			NTRD		NTID
Phenytoin	NTID		NTRD	CDD	NTID
Prazosin			NTRD		NTID
Primidone			NTRD		NTID
Procainamide			NTRD		NTID
Quinidine			NTRD	-	NTID
Sirolimus	NTID	NTID		CDD	NTID
Sulfonylurea compounds	-	^b	NTRD ^c	^e	NTID ^f
Tacrolimus	NTID	NTID	NTRD	CDD	NTID
Theophylline	NTID		NTRD ^d	CDD	NTID ^g
Valproic acid (divalproex sodium) ^a	NTID		NTRD		NTID
Warfarin	NTID		NTRD	CDD	NTID
Zonisamide			NTRD	-	NTID

empty cells Approved, but unlisted/no designation of NTID status (These substances have not been explicitly designated as NTIDs, as they may not yet have been evaluated by regulatory authorities, may still be under consideration, or may be deemed unnecessary for NTID designation);—Not approved or withdrawn post-market

Footnote: Some countries publish only the active substance name for NTIDs, without dosage form, route, or specific salt/carbonate information. To ensure consistency and comparability across jurisdictions, only the substance name is shown in this table

CDD critical dose drug, *EMA* European Medicines Agency, *FDA* Food and Drug Administration, *MFDS* Ministry of Food and Drug Safety, *NTID* narrow therapeutic index drug, *NTRD* narrow therapeutic range drug, *PMDA* Pharmaceuticals and Medical Devices Agency

^aValproic acid and divalproex sodium are considered the same substance, as both are based on valproate

^bReview of NTID designation and approval status for all sulfonylurea compounds in the NTID lists of Japan and South Korea showed that only glibenclamide, gliclazide, and tolbutamide have been approved; all are unlisted/no designation of NTID status

^cSulfonylurea antidiabetic compounds: acetohexamide, glibenclamide, gliclazide, glycopyramide, tolazamide, tolbutamide

^dTheophylline compounds: aminophylline, choline theophylline, diprophylline, proxiphylline, theophylline

^eReview of NTID designation and approval status for all sulfonylurea compounds in the NTID lists of Japan and South Korea found that only gliclazide is approved, and it is unlisted/no designation of NTID status.

^fSulfonylurea compounds: glibenclamide, gliclazide

^gTheophylline compounds: aminophylline, oxtriphylline (choline theophylline), diprophylline (dyphylline), proxiphylline, theophylline

NTID status could not be confirmed for four substances—Isoprenaline, Metaproterenol, Phenobarbital, and Procainamide—that appear in the Orange Book but are not searchable in the PSG database. This finding indicates that, although these drugs are FDA-approved, PSGs for these substances have not yet been issued, or they are not currently considered targets for generic drug development. Of the 38 substances analyzed, 13 were designated as NTIDs in the FDA's PSGs; all 13 were also consistently identified as NTIDs in both Donnelly *et al.* and Anno *et al.* (10, 11). No additional substances were classified as NTIDs beyond these 13, supporting the conclusion that, at present, only these 13 substances are confirmed as NTIDs in the FDA's PSG database. For the EU, approval status and NTID designation were identified using the EMA's "List of Union Reference Dates and Frequency of Submission of Periodic Safety Update Reports (PSURs)" and the EMA's PSGs. As with the FDA, the EMA does not maintain a separate NTID list, and NTID designations are provided within the PSGs. Consequently, NTID status could not be confirmed for 25 substances that are approved but not included in the PSGs. A flowchart illustrating the NTID designation and approval status for the 38 substances—representing the union of NTIDs across the five countries studied—is provided in supplemental 1.

Discussion

This review systematically compared regulatory approaches in five countries—the US, EU, Japan, Canada, and South Korea—regarding NTID terminology and definitions, the design of BE studies for generic drugs, BE evaluation criteria for generic NTIDs, and NTID lists. Regulations, guidelines, and relevant literature from each regulatory authority were reviewed to identify similarities and differences across countries. The findings demonstrate that, although all five countries recognize the NTID concept, notable discrepancies persist in NTID definitions, BE study design and evaluation criteria for generic NTIDs, and the composition of NTID lists.

Among the five countries, the EU and Japan do not provide official NTID definitions in their regulations or guidelines. In contrast, the US, Canada, and South Korea define NTIDs as drugs for which small differences in dosage or blood concentration may result in serious adverse effects or therapeutic failure. South Korea uniquely incorporates quantitative pharmacological and toxicological criteria—such as $LD_{50}/ED_{50} < 2$ or $MTC/MEC < 2$ —into its definition. This quantifiable approach not only differentiates South Korea's framework but also highlights the scientific rationale for more objective and reproducible NTID classification, reducing regulatory uncertainty in drug development. In practice, however, its application depends on the availability and

reliability of preclinical and clinical data, meaning that a drug may meet these ratios in theory but still require contextual judgment based on observed patient outcomes.

Regarding BE study design and evaluation criteria for generic NTIDs, the EU, Canada, and South Korea impose tighter acceptance limits for AUC_t and may optionally narrow limits for C_{max} , thus addressing NTID-specific concerns. AUC_t reflects overall drug exposure and therapeutic effect, and typically exhibits lower inter- and intra-subject variability (27). As deviations from the reference product may cause therapeutic failure or toxicity due to accumulation, a stricter limit is warranted. C_{max} represents peak plasma concentration, whose clinical relevance depends on drug characteristics and is more susceptible to physiological variability; consequently, a narrower limit for C_{max} is applied only when clinically justified, such as for drugs requiring TDM or with increased sensitivity to adverse effects. The US employs the most stringent approach for high-risk drugs like NTIDs, mandating a fully replicated four-way crossover design. The fully replicated design, in which each subject receives both test and reference products twice, enables precise estimation of intra-subject variability. This methodological choice is not only statistically robust but also scientifically meaningful, as it directly addresses the clinical concern of maintaining consistent therapeutic effects within the same patient over multiple dosing cycles. Nevertheless, the requirement poses significant practical burdens in terms of study duration, recruitment, and cost, which may affect its feasibility in routine generic development. Thus, the guidelines serve as fundamental scientific standards, but their implementation involves case-by-case regulatory judgment, achieving a balance between methodological rigor and real-world feasibility.

The most significant divergence among the five countries concerns NTID list provision and management. The disparities in NTID list availability and the number of designated substances arise from the lack of standardized selection criteria and the variability in how NTIDs have been defined by country, highlighting the potential benefit of adopting a more quantitative, objective definition, such as that used in South Korea. Designation requires consideration of multiple factors, including clinical risk, patient variability, therapeutic range, and TDM necessity (6). Additionally, a drug's risk profile may vary with formulation, dosage strength, and route of administration. Establishing definitive NTID lists risks omitting high-risk drugs not included; thus, some authorities prefer product-specific evaluations to avoid overgeneralization and potential exclusion of clinically relevant risks. Notable discrepancies are evident: Everolimus and Levothyroxine are NTIDs in the US, EU, and South Korea, but not on official lists in Canada or Japan. Similarly, Carbamazepine and Valproic acid are NTIDs in the US, Japan, and South Korea, but not in the EU or Canada. Such inconsistencies complicate multinational generic NTID development

and regulatory submissions. Variations in BE study requirements, dossier preparation, and regulatory costs may result in redundant processes, increased workload, and extended timelines. While NTIDs are generally selected based on pharmacokinetic and pharmacodynamic attributes, these criteria alone may not reflect real-world clinical outcomes. For example, a drug with a narrow therapeutic index may rarely cause adverse effects, whereas one with a wider range could still be associated with frequent side effects in clinical practice. It is also necessary to consider potential criticisms of a globally harmonized NTID list. Some countries may wish to maintain regulatory flexibility to reflect their national healthcare priorities, risk–benefit assessment, or acceptable levels of safety. Flexible standards may be necessary to accommodate the accumulation of new evidence, country-specific patterns of drug utilization, and pharmacogenomic variations that influence therapeutic response. Accordingly, an internationally harmonized framework should allow for periodic updates and provide mechanisms for jurisdictions to justify deviations based on scientifically sound rationales.

While it is now common practice to determine whether a new drug qualifies as an NTID based on its CTD, having a clearly defined NTID list still offers substantial practical benefits. Such a list enables more rapid and consistent consideration of NTID status during the development of generic drugs, thereby reducing regulatory uncertainty and facilitating timely decision-making. Furthermore, an internationally harmonized NTID list would enhance cross-jurisdictional regulatory alignment and support the global development of generic NTIDs. Accordingly, to reduce regulatory uncertainty and streamline global development of generic NTIDs, a reliable and internationally harmonized NTID list is needed. Such a list should integrate theoretical pharmacological criteria and real-world clinical data, including patient genetic variability and concomitant medication use, to better support patient safety and regulatory alignment. Establishing an internationally harmonized NTID list and a standardized management framework—integrated into global guidelines and encompassing BE study designs and evaluation criteria for generic NTIDs—would promote regulatory alignment, improve patient safety, and increase the reliability of generic NTIDs. Since 2019, the ICH has developed the M13 series (M13A, M13B, M13C) to set globally unified BE evaluation criteria. ICH M13A provides recommendations on the conduct of BE studies during development and post-approval phases for orally administered immediate-release solid oral dosage forms, whereas ICH M13B outlines the scientific and technical considerations for obtaining waivers of BE studies for additional strengths of a drug product once BE has been demonstrated for at least one strength. In particular, ICH M13C is intended to provide guidance on BE evaluation for highly variable drugs, drugs with a narrow therapeutic index, and studies involving complex BE study designs and data analysis.

Development of M13C commenced in February 2025, with official adoption (Step 4) planned for February 2029 (28). If the guideline incorporates both harmonized BE evaluation standards and a clear NTID definition with an internationally recognized NTID list, it could serve as a comprehensive reference for regulatory authorities worldwide. Such integration would reduce redundant efforts by stakeholders involved in the development, approval, and review of generic drugs. It would also enable more rapid regulatory decision-making based on harmonized criteria, ultimately improving timely patient access to high-quality, safe, and effective medicines.

Conclusion

This review presents a comparative analysis of NTID-related regulatory frameworks across major regulatory authorities and proposes key considerations for the development of ICH M13C, along with recommendations to facilitate global development and distribution of generic pharmaceuticals. Unlike previous studies that mainly examined the US FDA's regulatory approach to NTIDs, this research offers a comprehensive cross-country comparison, including NTID terminology and definitions, BE evaluation criteria for generic NTIDs, and NTID substance lists. Systematic organization and comparison of NTID-related policies across countries can provide foundational data for future development of harmonized global NTID guidelines. The advancement and expanded availability of generic NTIDs worldwide may reduce healthcare costs and improve access to essential therapies (29). However, the present study is limited by its primary focus on explicit regulatory criteria across countries, without extensive exploration of real-world applications or case studies. Furthermore, some countries employ a case-by-case approach rather than issuing official NTID lists, potentially limiting the objectivity and completeness of the comparative analysis. Future research should extend beyond national regulatory standards to include in-depth analyses of real-world case studies involving the approval and evaluation of generic NTIDs. Such efforts could yield more actionable insights and significantly contribute to the development of effective international guidelines and the advancement of global regulatory harmonization.

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Declarations

Conflicts of interest The authors declare no conflicts of interest.

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