



GENERIC DRUGS APPRAISAL AND APPROVAL:
DEPARTING FROM THE 'ONE-SIZE-FITS-ALL'
APPROACH

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction	INN	International Non-proprietary Name
ANDA	Abbreviated New Drug Application	NBCD	Non-Biologic Complex Drug
ANVISA	Agência Nacional de Vigilância Sanitária	NCE	New Chemical Entity
API	Active Pharmaceutical Ingredient	NDA	New Drug Application
BA	Bioavailability	NGO	Non-Governmental Organization
BE	Bioequivalence	NTI	Narrow Therapeutic Index
CMC	Chemistry, Manufacturing & Controls	PMDA	Pharmaceuticals and Medical Devices Agency
COFEPRIS	Comisión Federal para la Protección contra Riesgos Sanitarios	QbR	Question-based Review
DRA	Drug Regulatory Agency	R&D	Research & Development
EMA	European Medicines Agency	RLD	Reference Listed Drug
EU	European Union	TGA	Therapeutic Goods Administration
FDA	Food & Drug Administration	US	United States
GAO	Government Accountability Office	USP	United States Pharmacopeia
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use	WHO	World Health Organization

DEFINITIONS AND METHODOLOGICAL NOTE

Narrow Therapeutic Index (NTI) drugs / Critical Dose drugs: Narrow Therapeutic Index drugs, also referred to as Critical Dose drugs, are characterized by a steep dose-response relationship, which means that there is a short therapeutic dosing range between sub-therapeutic and toxic doses. This means that improper dosing, even by small amount, can lead to serious ADRs and even toxicity. For example, the chemotherapy drug 5-fluorouracil, the anticoagulant drug *Warfarin*, and the immunosuppressant drug Cyclosporine are all drugs with a narrow therapeutic index.

Non-Biologic Complex Drugs (NBCDs): Non-Biological Complex Drugs are chemical-based drugs whose Active Pharmaceutical Ingredient is composed of a complex structure of different yet closely-related nano-particles, as opposed to a small, homo-molecular structure. For example, the Multiple Sclerosis drug *Glatiramer Acetate*, the Anemia drug *Iron Sucrose* and *Liposome*-based drugs for treating breast and ovarian cancers are all considered as Non-Biological Complex Drugs.

Methodological Note: Throughout the report the terms “generic product” and “follow-on product” are used interchangeably, and refer only to chemical-based drugs, unless where stated otherwise.



EXECUTIVE SUMMARY

Generic medicines – follow-on versions of off-patent innovative medicines – are designed to be interchangeable to the innovative reference product. As more sophisticated and complex medicines are developed, securing the safe and effective use of their follow-on products becomes increasingly challenging.

Traditionally, DRAs in most developed and developing countries rely on innovative drugs' proven safety and efficacy when approving a follow-on product, which consists of the same dose and formulation of the reference drug's API. In this sense, generic drugs are not required to be exact copies of their reference products and they may differ in their composition in terms of the excipients used, release mechanism, and other aspects such as shape and color.

Over the last few years, there is a growing recognition of the inadequacy of this 'one-size-fits-all' approach in generic drugs approval. A growing body of scientific literature highlights the gaps and challenges within the regulatory process, posed by various types of drugs such as drugs with a NTI or drugs with complex molecular structure known as NBCDs. Indeed, research suggests that even small and seemingly insignificant changes to the determinants of follow-on versions of a NTI drug or an NBCDs can significantly affect these products' clinical outcomes and safe use, resulting in undesirable clinical outcomes, such as weakened efficacy, an increase in ADRs, and even toxicity.

Nevertheless, despite this growing recognition follow-on versions of NTI drugs and NBCDs continue to receive market approval under the conventional pathway for generic drugs in many countries.

Purpose and key findings

This report zeroes in on the existing gaps and challenges within the 'one-size-fits-all' model of generic drugs approval vis-à-vis NTI drugs and NBCDs, with the purpose of identifying the discrepancies between the state of the scientific drug regulatory literature and recommendations and actual practice within leading and developing DRAs.

It examines current drug regulations in seven DRAs from both developed and emerging markets.

The report's findings can be grouped along three key findings:

Key finding 1: NTI drugs and NBCDs necessitate a more rigorous regulatory approach

A growing body of scientific evidence now clearly indicates that the conventional, 'one-size-fits-all' approach in the regulatory approval of generic drugs is technically inadequate for ensuring the safe and effective use of follow-on versions to the reference product, especially with regards to NTIs and NBCDs.

With respect to NTI drugs, evidence suggests that small, seemingly insignificant changes to the drug's formulation, compound or excipients, undetected or unaccounted for by the current regulatory approval model, may, and indeed already have resulted in poorer efficacy and a wide range of adverse reactions, toxicity and unwarranted clinical outcomes. These concerns are compounded by the practice of generic substitution which exists in many countries today, yet often fails to address the health and safety challenges posed by generic versions of NTI drugs.

With respect to NBCDs, experts from across the board agree that the current analytical methods which are utilized for the appraisal of follow-on versions are incapable of full characterization of complex drugs and therefore cannot safely establish equivalence and interchangeability between an innovative complex drug and its follow-on versions. Thus, follow-on versions of complex drugs can only be deemed as 'similar' and not equivalent.

To ensure that generic versions of NTI drugs and NBCDs maintain the same safety, quality and efficacy properties of the reference product, scientific recommendations include the following:

NTI drugs

- A narrower range of 90-111% for determining bioequivalence, instead of the general 80-125%;
- Stricter bioequivalence trial design which ensures that the difference between the reference and follow-on products are negligible under the acceptable statistical validity;
- Maintaining a list of NTI drugs;
- Permit generic substitution of NTI drugs only under the conditions of switching in a highly-controlled manner, and with appropriate therapeutic monitoring for adverse drug reactions and toxicity.

NBCDs

- Follow-on versions of non-biological complex drugs should be appraised under the stepwise approach of the biosimilars pathway, where the follow-on product is developed through an iterative development to fit the process as similar as possible to that of the reference product, and its similarity is determined using a 'totality of evidence' which involves the state-of-the-art analytical methods as well as clinical studies;
- The follow-on version's interchangeability may only be established throughout the product's life-cycle, due to the sensitivity of the production process. As a result, generic substitution is discouraged or not recommended without the monitoring of a healthcare professional.



Key finding 2: DRAs have been slow in addressing the challenges posed by NTI drugs and NBCDs and patients potentially remain at risk

This report's mapping of the current practices for generic drug approvals for NTI drugs and NBCDs in seven developed and developing markets confirms that the 'one-size-fits-all' approach suffers from substantial gaps with respect to the current state of the scientific literature. Indeed, among the seven examined drug regulators (which include both stringent as well as developing DRAs) none has implemented in full (or even in part, in some cases) the recommended standards and practices for approving follow-on versions of NTI drugs and NBCDs.

For NTIs there has been some positive movement with five of the seven DRAs mapped introducing narrower bioequivalence bands of 90-112% for NTIs. Yet significant gaps still remain.

Conversely, for NBCDs no DRA has changed regulatory requirements and procedures for these follow-on products.

Interestingly, where these gaps and challenges are most striking is within the most stringent and advanced DRAs, namely the FDA and the EMA.

In the US NTI drugs still lack a formal definition, a federal-level list, and, most importantly, a narrower range of bioequivalence. While some generic versions of NTI drugs may and have been asked to undergo a stricter bioequivalence trial, this is determined only on a case-by-case basis. The *Generic Complex Drugs Safety and Effectiveness for Patients Act* was introduced to the US Congress in March 2015. The bill would require the Government Accountability Office to assess the FDA's ability to adequately appraise and evaluate follow-on versions of NBCDs. The bill also asks the Office to assess whether the biosimilars approval pathway (section 505(j) of the FD&C Act) would be a more appropriate mechanism for the regulatory approval of follow-on versions of NBCDs. While this proposed legislation is being debated the FDA has allocated funds for research into the equivalence of follow-on versions of NBCDs that are already marketed, and to which compendial monographs are still in development.

In the EU, generic drugs manufacturers are increasingly using the decentralized procedures for approving their products. Thus, while the EMA itself maintain stricter requirements for approval of follow-on versions of NTI drugs and NBCDs, follow-on products can be authorized for marketing in one Member State with less-strict regulations, and gain access to the entire EU market via the mutual recognition procedure.

Key finding 3: Regulatory convergence is taking place – Next step should include NTIs and NBCDs

The regulatory approval process for generic drugs – which includes standards governing bioequivalence and labeling to manufacturing and dispensation – is in most major respects converging. Since the mid-1980s and passage of the Hatch-Waxman Act in the US, most major DRAs have introduced similar pathways for follow-on products. Generic drugs are required to provide bioequivalence data that underpin the assumptions about pharmaceutical and therapeutic equivalence between reference and follow-on product and their safe and effective use.

As mentioned, five of the seven DRAs examined in this report have taken partial measures strengthening regulatory requirements for NTIs. The WHO and other international institutions are also working on improving best practices for the approval of generic follow-on products. Once a growing body of DRAs introduce reforms to both the approval process for NTIs and NBCDs there is a good chance this can become an established international best practice and regulatory convergence is more likely to take place.



INTRODUCTION

Generic medicines – follow-on versions of off-patent innovative medicines – are designed to be interchangeable to the innovative reference product. As more sophisticated and complex medicines are developed, securing the safe and effective use of their follow-on products becomes increasingly challenging.

Traditionally, DRAs in most developed and developing countries rely on innovative drugs' proven safety and efficacy when approving a follow-on product, which consists of the same dose and formulation of the reference drug's API. In this sense, generic drugs are not required to be exact copies of their reference products, and they may differ in their composition in terms of the excipients used, release mechanism, and other aspects such as shape and color.

The issue

Over the last few years, there is a growing recognition of the inadequacy of this 'one-size-fits-all' approach in generic drugs approval. A growing body of scientific literature highlights the gaps and challenges within the established regulatory approval process, posed by various types of drugs such as drugs with a NTI or drugs with complex molecular structure known as NBCDs. Indeed, research suggests that even small and seemingly insignificant changes to the determinants of follow-on versions of a NTI drug or NBCDs can significantly affect these products' clinical outcomes and safe use, resulting in undesirable clinical outcomes, such as weakened efficacy, an increase in ADRs, and even toxicity.¹ As this study highlights there is a growing body of evidence questioning generic drug candidate's equivalence to the reference product for NTIs and NBCDs and potential health and safety risks these products pose.

In this light, stringent DRAs and international institutions including the WHO and the ICH have invested increasing efforts into addressing the gaps in the regulatory framework of generic drugs approval and securing the safe use of generic drugs by harmonizing best practices and ensuring they are taken at both the national and international level. The EMA has been given the lead role in the WHO's International Generic Drug Regulators Pilot program; a global project aimed at converging the best practices for generic drug approval in order to construct an international network which would

enable DRAs to share information on the appraisal of generic medicines.²

Nevertheless, despite this growing recognition and efforts at individual DRAs (discussed in more detail below) follow-on versions of NTI drugs and NBCDs continue to receive market authorization under the conventional pathway for generic drugs in many countries.

This report zeroes in on these existing gaps and challenges within the 'one-size-fits-all' model of generic drugs approval vis-à-vis NTI drugs and NBCDs, with the purpose of identifying the discrepancies between the state of the scientific drug regulatory literature and recommendations and actual practice within leading and developing DRAs.

The report consists of three sections:

Section 1 provides a broad and detailed discussion of the approval process for generic drugs and identifies the gaps and challenges posed by the market entry of follow-on products for NTI drugs and NBCDs. The section reviews the current scientific research and thinking on the 'one-size-fits-all' model for generic drug approval, and examines the specific recommendations for changing the appraisal of follow-on versions of NTI drugs and NBCDs. What are the risks with the current "one-size-fits-all" model for approving follow-on products and how can DRAs around the world improve existing regulations?

Section 2 provides a comparison of the regulatory pathways for approval of generic drugs in seven developed and developing countries focusing on the regulatory standards in place for NTI drugs and NBCDs.

Section 3 offers an overview of the key findings of the report and concluding thoughts on what can be done to secure the integrity of generic drugs and ensure their safe and effective use by patients around the world.



1

ENSURING SAFETY, QUALITY AND EFFICACY IN THE GENERIC DRUG APPROVAL PROCESS

How are generic follow-on products approved or market? And how does the approval process for generic drugs differ from innovative, reference products?

1.1 Framing the context – the generic approval process

To be approved for market innovative medicinal products must undergo rigorous testing and provide substantial proof of their safety, quality and efficacy – the three 'essential pillars' of the regulatory approval process.³ The safety and efficacy of the drug candidate is demonstrated in pre-clinical and clinical trials data, which is reviewed by regulatory authorities prior to market approval. Although review standards can vary across the world with the most stringent drug authorities using high-level harmonized standards, such as those set by the ICH, the basic R&D process for developing biopharmaceuticals remains similar regardless of where in the world a product is being developed.⁴ Figure 1 details the biopharmaceutical R&D process.

As Figure 1 illustrates, drug development is not easy and is a long cumbersome process often taking a decade or more to complete. Figure 1 shows the R&D process for developing new, innovative medicines. Generic drugs, however, are not required to undergo a similar process. Instead, in most countries the review process is abbreviated and a generic follow-on product can rely on the previously submitted safety and efficacy data by an already approved reference product. This is frequently referred to as an abbreviated approval pathway. Because of the existence of pre-existing safety and efficacy information the approval process is made shorter, abbreviated, for follow-on products. This saves time and money and ensures that patients and consumers of medication are able to gain quick access to cheaper generic products as soon as any form of market exclusivity (such as that conferred by patent protection or regulatory data protection) expires. In this sense, it is instructive to look at the procedures and

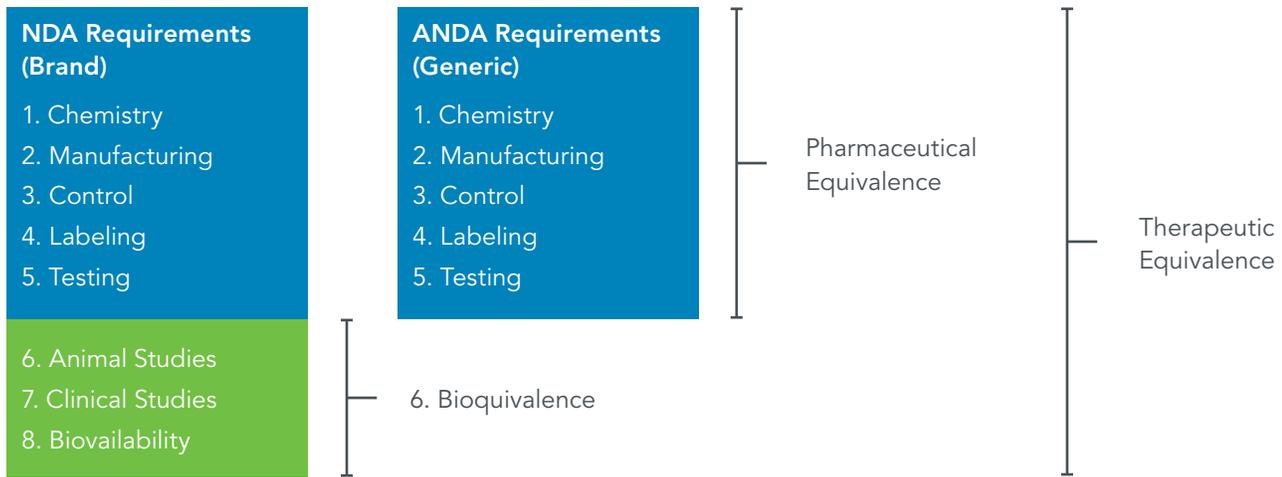
requirements in place in the largest and most advanced biopharmaceutical market in the world, the US.

Since the enactment of the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act), generic drug manufacturers in the US have been allowed to submit so called ANDAs for marketing approval of follow-on products. The ANDA pathway is a designated regulatory pathway for generic drugs approval which is significantly condensed compared to the approval process for innovative drugs. Similar pathways are in place within the majority of DRAs around the globe. Important exceptions exist in some countries, particularly in Latin America, where a third type of product is on the market, so-called *similares*. As will be discussed below these products are in essence copies of branded, reference products that do not need to undergo the same type of bioequivalence or bioavailability testing that a generic follow-on product does. While they are still prevalent, many Latin American countries have over the last fifteen years introduced regulatory reforms that would in effect remove these products from the market, requiring that all follow-on products on the market be bioequivalent to a reference product.

The primary requirement for an ANDA is that the generic drug candidate demonstrates proof of bioequivalence to the innovative "Reference Listed Drug" or 'reference product'. Figure 2 outlines the requirements within the approval process comparing an ANDA application with a NDA application.

FIGURE 1 The biopharmaceutical R&D process

FIGURE 2 Comparing FDA approval process requirements for NDAs and ANDAs



ANDAs are not required to:

- Perform safety and efficacy studies
- Use the same excipients
- Maintain the same level of post-marketing surveillance

Source: Johnston, A. (2013), Martin, C. (2011)

As depicted above in Figure 2, the approval process for generic drug candidates consists of two levels.

First, generic drug candidates must exhibit *pharmaceutical* equivalence to their reference product, which means that they must “contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration”, according to the FDA’s definition.⁵ *Pharmaceutical* equivalence is determined through meeting compendial standards and having the same labeling standards.

Second, generic drug candidates must demonstrate surrogate *therapeutic* equivalence, which requires that the generic drug candidate undergo bioequivalence studies. These studies provide the FDA with proof that the generic drug candidate “can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling”.⁶

As a result, to receive market approval by the FDA generic drugs are not required to be exact copies of their reference products.

Indeed, according to the FDA, generic drugs “may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling”.⁷

What is bioequivalence?

Bioequivalence can be regarded as a similarity assessment test of a generic drug to its reference product.⁸ It is a fundamental component of the generic approval process and used to provide proof of a generic follow-on product’s interchangeability with a reference product.

In BE trials, the bioavailability – the rate and extent of a product’s active ingredient absorption within the bloodstream – of the generic drug candidate

and of the reference product is measured by a set of predefined parameters within a small-scale randomized clinical trial of usually 12-50 healthy volunteers.⁹ (There are exceptional cases where equivalence can be sufficiently demonstrated within laboratory conditions, known as *in vitro* studies, and there is no need for a clinical trial on human subjects.¹⁰)

Bioequivalence between a generic drug candidate and its reference product is demonstrated when, according to the FDA: “the rate and extent of absorption of the test drug do not show a *significant difference* from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions”.¹¹

Within most DRAs (including stringent ones such as FDA and EMA) this “significant difference” is only evident in cases where the bioavailability of the generic drug candidate differs from that of the reference product by more than 20%.

This means that a generic drug candidate is typically considered bioequivalent to the reference product if its absorption rate within the bloodstream is within the similarity limits of 80%-125% to that of the reference product. In other words, one follow-on product can have an absorption rate of 81% and another can have an absorption rate of 124% compared to the reference product yet for all intents and purposes the products are considered bioequivalent to the reference product.

It should be noted that there are numerous factors that can affect a given drug’s bioavailability. Product-related factors include the physical and chemical properties of the drug, such as the drug’s purity, potency and stability, and its uniformity with respect to color, shape, size, etc.¹² These factors are determined and affected by the manufacturing, labeling, distribution and dispensation processes. Impurities within the production lines, inadequate temperature control during distribution, improper labeling – all can impact the bioavailability of a given generic product.¹³ Patient-related factors, such as concurrent diseases and medication, gastrointestinal characteristics (e.g. pH, blood flow

and bacterial flora) and differences in metabolism may also affect a drug’s bioavailability.¹⁴

Generic drugs regulatory approval – a global ‘one-size-fits-all’ approach?

Since the introduction of the Hatch-Waxman Act the regulatory appraisal and approval process of generic drugs has bolstered and improved greatly not only in the US but also in many other developed and developing countries. The evolution of new technologies has also provided drug regulators with better tools for understanding the differences in characteristics between a generic drug candidate and the reference product.¹⁵

Indeed, the strong scientific and statistical basis for determining bioequivalence has shaped the underlying rationale of the ANDA process: **that generic products classified as *therapeutically equivalent* to the reference product – i.e. both *bioequivalent* and *pharmaceutical equivalent* – are interchangeable with the full expectation of producing equivalent clinical outcomes, within the same safety profile of the reference product.**¹⁶

While there are still considerable differences between drug regulators – not least between stringent regulators and DRAs in many emerging and developing markets – this basic recognition or assumption of equivalence has shaped drug regulations at most of the major pharmaceutical markets in the world which have in place similar protocols and requirements as captured in Hatch-Waxman.

Table 1 on the following page lists some of the regulatory requirements in generic drug approval within 14 regulatory authorities across the world.

TABLE 1 Guidelines for bioequivalence of generic drugs – a comparison of 14 drug regulatory agencies

	TGA (AU)	ANVISA (BR)	HC (CA)	SFDA (CN)	EMA (EU)	CDSCO (IN)	MHLW (JP)
Generic product must be <i>pharmaceutically</i> equivalent?	✓	✗	✓	✓	✓	✗	✓
A 2-period crossover BE study design	✓	✓	✓	✓	✓	✓	✓
Is there a requirement for proportionality between male/female subjects?	No	Yes	No	Drug-specific	No	Yes	No
Minimum number of volunteers	12	12	12	18-24	12	16	–
Acceptable age range	>18	18-50	18-55	18-40	>18	>18	>18
Is there a requirement for <i>fasting</i> and <i>fed</i> condition BE studies?	✓	✓	✓	✓	✓	✓	✓
Acceptable BE range for single-dose studies	80-125%	80-125%	80-125%	80-125%	80-125%	80-125%	80-125%
	COFE PRIS (MX)	HSA (SG)	KFDA (KR)	Swiss medic (CH)	FDA (US)	WHO (UN)	SADC (ZA)
Generic product must be <i>pharmaceutically</i> equivalent?	✗	✓	✓	✓	✓	✓	✗
A 2-period crossover BE study design	✓	✓	✓	✓	✓	✓	✓
Is there a requirement for proportionality between male/female subjects?	No	No	No	No	No	No	No
Minimum number of volunteers	24	12	12	12	12	12	12
Acceptable age range	18-55	18-55	19-55	>18	>18	18-55	18-55
Is there a requirement for <i>fasting</i> and <i>fed</i> condition BE studies?	✓	✓	✓	✓	✓	✓	✓
Acceptable BE range for single-dose studies	80-125%	80-125%	80-125%	80-125%	80-125%	80-125%	80-125%

Adapted from: Davit, B. et al, 2013; Kaushal, N. et al, 2016; analysis: Pugatch Consilium

Legend: AU – Australia; BR – Brazil; CA – Canada; CN – China; EU – European Union; IN – India; JP – Japan; MX – Mexico; SG – Singapore; KR – South Korea; CH – Switzerland; US – United States; UN – United Nations; ZA – South Africa.

Table 1 clearly shows how, despite minor differences between them, most major DRAs adhere to internationally-accepted standards of determining BE for generic products, thus maintaining a fairly similar generic drug regulatory approval process. This model is utilized for follow-on products of all types of drugs, in a ‘one-size-fits-all’ manner.

Critically, for NTI drugs and NBCDs, no distinct pathway exists nor internationally accepted standards or even consensus among DRAs (stringent or otherwise) regarding the best methods for ensuring their safety and efficacy. Instead, as will be shown below in Section 2, DRAs differ significantly in their approaches to approval of follow-on products of these types of drugs. Indeed, few DRAs officially recognize the special safety requirements that NTIs and NBCDs require and even fewer have specific protocols of approval for these types of products.

The next two sub-sections provide a more detailed discussion of the specific gaps and challenges in the ‘one-size-fits-all’ approval pathway for follow-on products both generally and particularly vis-à-vis NTIs and NBCDs.

1.2 Challenges necessitating a more rigorous approval process for generic drugs

While requiring bioequivalence tests to fall within the limits of 80%-125% has become standard practice at many DRAs, accumulated evidence from numerous clinical and pharmacological studies suggests that in practice, even within these limits a generic version of a given drug can vary significantly from other versions of the same drug as well as from the reference product.¹³

Generic drift

The primary challenge to the current regulatory model for treating all follow-on products the same concerns cases in which the BE range between two products may actually be larger than the accepted range of 20%. Since BE limits are set at 80%-125%, there is significant room for difference between the reference product and generic product, as well as between two generic products determined to be bioequivalent to a reference product.

To illustrate, consider two generic products: one that is bioequivalent to the reference product at 86% and another at 115%. Both are bioequivalent to the reference product, as they reside within the 80%-125% BE limits. However, if they were to be compared between themselves in a BE trial (where one of the generic products is the reference product), the difference in bioavailability between the two products would be larger than 20%. In this case, the two generic products would not be bioequivalent.¹⁸ This phenomenon is known as “generic drift”.¹⁹

In most DRAs BE studies compare the generic drug candidate to the reference drug, and not to other follow-on products on the market.²⁰ Studies show that usually the first and second follow-on products are bioequivalent both to the reference product and to each other but that later follow-on products can be outside this range when compared to other generic products.²¹ Therein lies a potential safety risk, especially for patients that received the innovative reference drug at the beginning of their treatment cycle and were subsequently switched to a follow-on product and then switched again to a different follow-on product.

The ‘generic drift’ risk is significantly amplified when looking at generic NTI drugs whose effect in the body varies little over time (known as low “within-subject variability”). If a generic NTI drug shows high within-subject variability in a BE trial, it is likely to show poorer efficacy and increased ADRs in real-time use, and therefore would probably not be approved for marketing.²² However, interestingly, generic NTI drugs with low within-subject variability may still differ by more than 10% from their reference product in bioavailability terms. The outcome is paradoxical: while generic NTI drugs with low within-subject variability fall within the class of drugs for which there is the greatest concern with “generic drift”, this is also the class of drugs for which there are fewer safeguards against the phenomenon.²³ Thus, the risk of unwarranted clinical outcomes and ADRs that could result from the use of generic NTI drugs is amplified among those with low within-subject variability.

This is a critical safety issue that DRAs have only recently begun to recognize. For example, as is discussed in more detail in section 2,

this recognition has led the FDA's technical committee in 2011 to establish that NTI drugs represent a distinct group of products, for which the BE standards are insufficient. Yet, to date, no distinct regulatory pathway for these products has been established.²⁴

These concerns are compounded by the fact that evidence on safety and efficacy of generic substitution of NTI drugs is scarce and inconclusive.²⁵ For example, while some studies have concluded that the generic version of the immunosuppressant drug *Cyclosporine* (an NTI often used in conjunction with organ transplants) is equivalent to its reference product,²⁶ others have shown significant disparities in clinical outcomes between a generic and the reference product as well as between two generic products.²⁷ Indeed, a number of empirical studies document an increase in acute first and second rejections among transplant patients upon switching from brand to generic *Cyclosporine*-based products.²⁸

In another example, a study found that switching to an equivalent generic formulation of the NTI drug *Carbamazepine* (an anticonvulsant used to treat seizures) increased the relative risk of neurological ADRs by nearly 50%. The study concluded that one of the parameters used for determining bioequivalence was not sufficiently sensitive for capturing small yet clinically relevant differences.²⁹

The risks of NTIs is a topic of intense debate within the scientific and regulatory community. For example, an expert committee of the FDA has promoted the use of a scaled average method for NTI drugs, where the BE range is determined by the reference product's variability. In a simplified manner, low variability entails a narrower BE range; high variability entails a wider BE range, within the confinements of the 80-125% limits.³⁰ Alternative approaches are also suggested which mainly involves the tweaking of different parameters examined in a BE trial.³¹

The need for a stricter, more rigorous approach for appraisal of follow-on versions of NTI drugs is acknowledged in the scientific community, and the narrower range of 90% to 111%-112% in bioavailability is widely accepted.³²



Bioequivalence trial design

A second concern with the current regulatory model relates to BE trials design, and the fact that current trial design standards often do not capture whether a given drug has different clinical outcomes depending on the type of patient and the timeframe of usage. As mentioned, BE trials are usually conducted in the form of a randomized and controlled clinical trial on 15-50 healthy volunteers. In these trials a set of parameters is tested in order to compare the relative bioavailability of the generic drug candidate to that of the reference product.

However, under this model, BE trials do not consider several factors which may affect the drug's safety and efficacy in prolonged use and which may not be derived from reliance on data for the reference product. For example, different populations (such as children and women) are generally not considered in full nor are factors such as age and co-morbidities.³³ As the preceding Table 1 illustrates, most DRAs do not require maintaining an equal proportion between male and female subjects. Worse, in some jurisdictions, such as Mexico, a requirement to use only



subjects of one sex is in place, intended to avoid gender-related differences in pharmacokinetics.³⁴ Additionally, since these trials are conducted within a relatively short period of time and are based on a single-dose design, long-term effects that may occur with chronic dosing may not be adequately captured.³⁵

These issues raise concerns as to whether results from BE trials can be generalized into demonstrating a generic drug's safety and efficacy. As with the challenge of 'generic drift' such concerns are particularly amplified with regards to more complex drugs, such as NTI drugs and NBCDs.³⁶ This concern is based on the fact that BE trials are not performed on patients who experience the targeted disease nor do they consider different racial groups, food and drug interactions and co-morbidities. This is important as there is evidence to suggest that these factors can significantly affect clinical outcomes in NTI drugs. For example, studies have shown that certain NTI drugs present different pharmacokinetic parameters when taken together with certain types of food. For example, one particular immunosuppressive

NTI follow-on product presented significantly different bioavailability parameters in comparison to the innovative product when consumed with apple juice.³⁷ In this case this negative interaction affected the follow-on product's efficacy and led to denial of market authorization in the EU. Conversely, the product was approved for market in the US and resulted in a massive recall after an FDA investigation.³⁸

It is for these reasons that various medical associations and patient groups, such as the American Heart Association and the CML Advocates Network, have recommended that special consideration be given to generic substitution of NTI drugs.³⁹ The American Kidney Foundation and the American Society of Transplantation have also issued recommendations that emphasize the need for a stricter BE trial design, inclusion of patients from different sub-populations, and using appropriate monitoring techniques.⁴⁰

One approach derived from these recommendations places a stricter, more rigorous BE trial design for generic NTI drugs, such as a

fully replicated 2-sequence, 2-treatment, 4-period crossover study design. This approach focuses on one of the main characterizations of an NTI drug – its low within-subject variability – and ensures that the difference between the reference and follow-on products are negligible.⁴¹ **However, as discussed below in section 2 very few DRAs have introduced or implemented a requirement for a stricter, more rigorous BE trial design in approving generic NTI drugs.**

Inadequate ability for full characterization

The release mechanisms and therapeutic action of complex drugs are different from the direct and systematic interactions of small molecule drugs. Because of this, even the slightest differences in their release or formation rate can have negative effects on drug safety and efficacy.⁴² In this respect, some NBCDs are more similar to other large and complex drugs such as biologics. However, while biological follow-on products, mostly referred to as *biosimilars*, are evaluated using distinct and stringent guidelines (often including the submission of individual clinical trials data more akin to a new drug application than that for a traditional follow-on product),⁴³ many follow-on products of NBCDs are classified as generics, and subject to the same BE trials as small molecule drugs.

This has led to increasing concerns regarding the adequacy of current BE standards in determining bioequivalence of generic NBCDs.⁴⁴ This inadequacy is manifested by the inability of current analytical methods to successfully isolate, quantify and characterize the nano-particles which comprise the NBCDs' API, as well as the different pharmacokinetics of these drugs.⁴⁵ These two factors – the full characterization of the API and its pharmacokinetics – are crucial to the process of determining bioequivalence. Gaps in this kind of knowledge limit the ability to accurately determine bioequivalence of generic versions of these drugs. For example, the US market entry of a follow-on product to the complex drug *Glatiramer acetate* (used to treat multiple sclerosis) has required nearly 50 highly comprehensive and complex analyses in addition to independent testing by the FDA in order to provide sufficient proof of bioequivalence to the reference product.⁴⁶

Expert opinion appears to be in agreement on this issue. For instance, a convention of experts from industry, academia and regulatory bodies at the 2012 FIP Centennial Congress agreed that the conventional model for generic drug approval is significantly lacking with respect to NBCDs.⁴⁷ Specifically, even the most advanced analytical means do not enable a complete structural characterization of the drug, and the acceptable parameters are insufficient in determining BE and clinical outcomes.

Based on these experiences, one prominent recommendation is that follow-on versions of NBCDs should be evaluated and approved under biosimilars pathways similar to what is in place at both the FDA and the EMA.⁴⁸ This pathway maintains a stepwise approach where the biosimilar product is developed to fit the process as similar as possible to that of the reference product. In addition, similarity is determined using a 'totality of evidence' defined as: "the scientific principle that establishes biosimilarity by using an extensive set of decisive methods sensitive enough to detect relevant differences, if present. These methods involve a large battery of state-of-the-art physicochemical, analytical, and functional methods and clinical studies".⁴⁹ The 'similarity' perspective entails that the follow-on version's comparability and interchangeability with the reference drug may only be established throughout the product's life-cycle, due to the sensitivity of NBCD development and production process. In line with this approach, generic substitution is discouraged⁵⁰ and not recommended without the monitoring of a healthcare professional.⁵¹

1.3 Ensuring the safety and efficacy of generics throughout the pharmaceutical life-cycle

Alongside the challenges discussed in the preceding sub-section which are specific to the approval process for generic follow-on products, both scale-up and manufacturing can significantly affect a follow-on product's properties and their safe and effective use. This is particularly the case for NBCDs and NTI drugs, whose characteristics and sensitivities necessitate closer monitoring in order to avoid unnecessary safety risks.

Monitoring generics' safety and efficacy during scale-up and manufacturing

The first element concerns a drug's scale-up and manufacturing process. As part of this process, an approved drug's formulation is tested for its ability to maintain its safety, quality and efficacy properties when manufactured on a mass-scale. While manufacturers are responsible for producing products to the highest quality and adhering to GMP standards the overarching responsibility for safeguarding the quality and integrity of a medicine lies with each individual DRA.⁵² These authorities are responsible for overseeing all actors and processes involved in manufacturing a medicine and ensuring that its quality is not allowed to deteriorate at any point during the production process.⁵³

One example of an issue that DRAs monitor is a change to a drug's formulation. During the manufacturing process, a drug's production is scaled-up to mass production of billions of units, and often there is a need to implement adjustments to the drug's formulation in order to, for example, improve its stability. Recently there has been a growing recognition that small and seemingly insignificant changes in the manufacturing process of drugs (such as different oils for liquid and capsule forms of the same product) can significantly affect a drug's efficacy and safety and cause undesirable clinical outcomes.⁵⁴

The importance of ensuring the safety and quality of drugs within the scale-up and manufacturing stage has led DRAs in many developed countries to shift increasing attention to this issue. For example, in the early 1990s both the FDA and the US Pharmacopeial Convention did not view changes to non-critical excipients as requiring deep regulation: "certain compositional adjustments (to formulations) were determined to be acceptable, without further justification".⁵⁵ This shifted in the late 2000s with the FDA issuing newer guidelines that categorized possible changes to the scale-up and manufacturing process in accordance with their potential to result in ADRs. According to these guidelines, formulation or excipients changes were (and remain) categorized as a "major change" which

requires prior-approval supplement filing.⁵⁶ Similar requirements are found in the EMA's guidelines on "post approval change management protocols".⁵⁷

Yet with regards to NBCDs and NTIs there are still significant gaps in what is judged to be critical information and a regulated process. For example, a recent 2014 white paper issued by the pharmaceutical industry criticizes the FDA's guidance for not providing "recommendations on specific information required to assess the effect of changes to identity, strength, purity, or potency of a drug product".⁵⁸ This is of particular importance to generic NBCDs and NTI drugs.

For NBCDs, which cannot be fully characterized by physicochemical analysis, it is crucial that the manufacturing process will maintain the complex drug's exact properties and characteristics, since even the slightest differences in its release or formation rate can have negative effects on the drug's safety and efficacy.⁵⁹

For NTI drugs, the use of different excipients can amplify unnecessary safety risks. For example, clinical data has shown that a 10% decrease in the concentration of an anti-epileptic drug may cause patients to suffer breakthrough seizures.⁶⁰ In addition, as mentioned above generic versions of the NTI anticonvulsant drugs *Carbamazepine* and *Gabapentin* have caused increased seizures in patients and more neurological side effects than the reference product.⁶¹ This phenomenon led the American Academy of Neurology to publish a position statement in 2007, stating that "the Food and Drug Administration has allowed for significant differences between name-brand and generic drugs... For anticonvulsant drugs, *small variations in concentrations between name brands and their generic equivalents can cause toxic effects and/or seizures when taken by patients with epilepsy.*"⁶²

Monitoring generics' safety and efficacy in distribution and post-marketing

Generic substitution

As part of the mass production and manufacturing of follow-on products there is also the issue of mass consumption of follow-on products. Each country (and in the US each individual state) have

rules and regulations in place that guide the dispensation of all prescription drugs including follow-on products. Critically, the protocols and formularies for pharmaceutical dispensation do not always take into account the above cited risks and differences between bioequivalence and concomitant clinical and therapeutic effects for follow-on products. Again, this is an issue of particular importance for NTIs and NBCDs.

For example, generic substitution, or automatic substitution (which refers to the switching of a prescribed innovative drug with its follow-on product, usually without first obtaining the health care provider or patient's consent) is a frequently used cost containment tool in a growing number of developed countries.⁶³ It is a policy used in most EU countries and across the US. Critically, substitution policies often mean that a patient can be switched, often unknowingly, from one follow-on product to another with the same prescription when refilling their prescriptions. While most markets have in place strong policies requiring

patient consent when switching, in practice this is often not the case. Overall, the commercial and regulatory incentives in place in a given market will have an impact both on the substitution policies in place but also, and this is critical, on the actual practices at the dispensation level. For example, are patients rigorously informed and made aware of the substitution of their medicines from one product to another? In many markets the manner in which policies are followed will vary from pharmacy to pharmacy.

With regards to NTI drugs in the US numerous medical associations recognize that substitution practices should be performed in a controlled manner and with appropriate therapeutic monitoring for adverse drug reactions and toxicity.⁶⁴ For example, the generic versions of the NTI antipsychotic drug *Clozapin* have resulted in relapses after generic substitution.⁶⁵ Indeed, the practice of generic substitution involving NTI drugs is illegal in some US states, such as North Carolina; other US states as well as EU countries



impose several restrictions on generic substitution of NTI drugs, including requirements for close monitoring.⁶⁶ Yet this is in practice complicated when countries or regional or state level jurisdictions differ on what is an NTI. In the US, for instance, state-level lists of NTI drugs may contain drugs not recognized as NTI drugs by the FDA.⁶⁷

In addition, since some NTI drugs are intended for long-term use (by oncology or organ transplant patients, for instance), some developed countries have composed lists of marketed NTI drugs that should be monitored with a higher degree of attention.⁶⁸ However, these lists vary greatly between countries, regions and private bodies, such as health insurers. For example, leading DRAs including the FDA, the EMA, Health Canada, and Japan's PMDA all widely recognize drugs such as *Digoxin* and *Warfarin* as NTI drugs, but differ with respect to other drugs such as *Tacrolimus*, *Carbamazepine* and *Phenytoin*.⁶⁹

Labeling

Another critical post-marketing issue concerns the labeling of follow-on products. In most countries today generic manufacturers are required to label their follow-on products with the same safety information as the reference product. The underlying logic is that if the follow-on product is bioequivalent to the reference product – resulting in the same clinical and therapeutic effect – then the identical safety information should apply to it as to the reference product.

Yet this assumption both ignores the fundamental differences outlined above with regards to the potential differences in manufacturing and ingredients in follow-on products versus a reference product as well as the manner in which safety information was gathered in the first place. Safety information is primarily gathered and analyzed from post-marketing surveillance (also known as phase IV clinical trials) which are performed predominantly on the innovative reference product. These studies are intended to safeguard larger scale use of the drug by monitoring any adverse effects that become evident as well as identifying what appears to be the most appropriate and effective manner of use.⁷⁰ However, while post-marketing trials are of

great importance, they are conducted mainly on innovative drugs (the reference products), and the incentive for the innovator to continue the monitoring over ADRs diminishes greatly upon market entry of follow-on products.

Thus, the acquiring of safety information from real-world use is limited for follow-on products.

In the US, in the wake of the Supreme Court's ruling exempting generic manufacturers from revising their products' labels in accordance with newly acquired safety information by the innovator, the FDA has proposed a rule that would permit generic drug manufacturers to update the labelling and safety information for their products individually.⁷¹ This potential new rule is however under consideration and a potential issuing has been pushed from 2016 to 2017.⁷²

The US is not the only major market that does not distinguish between the safety and labelling information for generic and reference products. For example, in the EU certain drugs that necessitate special monitoring are required to display a black triangle in the package leaflet and in the summary of the product's characteristics under Regulation 198/2013.⁷³ This measure is part of a comprehensive pharmacovigilance law that took effect in the EU in 2012 and has resulted in an increase of 30% in ADR reports during 2013.⁷⁴ However, critically this regulation refers only to innovative products and not to generics.⁷⁵

Summary

Taken together, the numerous challenges and examples presented in this section emphasize the need for taking a nuanced, more rigorous approach to the approval of generic drugs throughout the entire drug's life-cycle. Indeed, there is a growing understanding within the scientific community that the classic 'one-size-fits-all' approach for generic drugs approval is insufficient to ensure the safety, quality and efficacy of marketed drugs.⁷⁶ Table 2 below outlines the gaps and challenges within the regulatory approval process of generic drugs as discussed above, both generally and vis-à-vis NTI drugs and NBCDs.

TABLE 2 Key international gaps and challenges in ensuring safety and efficacy of generic drugs throughout the life-cycle vis-à-vis NTI drugs and NBCDs

Life-cycle stage	Key gaps and challenges	Description	Clinical implications for NTI drugs / NBCDs
Appraisal and approval stage	Acceptable BE range permits differences between products; causes "generic drift"	Follow-on products are tested for BE against the reference product. Market entry of multiple generic products increases risk of significant differences in BA between products	NTI drugs and highly-variable drugs are highly vulnerable to "generic drift" and are highly sensitive to seemingly insignificant changes which can result in poorer efficacy, ADRs and toxicity
	BE trial design requirements do not capture 'real-world' variances	By and large, regulatory requirements for BE trials design do not address: <ul style="list-style-type: none"> • Lack of proportionality between male/female subjects • Lack of representation of different populations (i.e. ethnic variance, age, etc.) • Potential risks of prolonged use • Potential risks associated with co-morbidities and drug-drug interactions • Potential risks associated with food-drug interactions 	Studies show that certain NTI drugs are especially sensitive to drug-drug and food-drug interactions, which may lead to decreased efficacy, adverse reactions, and unwarranted clinical outcomes
	Incapacity for full characterization of complex drugs	Current analytical methods used for determining bioequivalence cannot fully characterize the differences between the reference and follow-on products of complex drugs	The inability of current analytical methods to fully characterize the API of complex drugs and their pharmacokinetic parameters seriously limit accurate determination of BE of NBCDs' follow-on products
Scale-up & manufacturing stage	Regulatory guidelines do not always convey the specific information required to assess the effect of changes to identity, strength, purity, or potency of a drug product	Implementing changes to a drug's formulation during scale-up process, and using different excipients, can significantly affect a drug's safety and efficacy	Certain types of drugs, including NTIs and NBCDs, are extremely sensitive to change; even slight differences in release or formation rate can affect safety and efficacy
Dispensation stage	Generic substitution regulations greatly differ between countries and within them, such as in the US	Switching from an innovative drug to a follow-on product is allowed, usually without the physician and patient's explicit awareness and/or consent	While generic substitution in NTI drugs requires a high degree of monitoring, lists of NTI drugs vary between (and sometimes within) countries, leading to a potential postcode lottery of safety risks, and compromising the traceability of ADRs
	New safety information not necessarily introduced promptly, if at all, into generic drugs' leaflets and labelling	Since post-marketing trials are conducted mostly by innovators, the period for acquiring 'real-world' safety information is limited Requirement for uniformity in labeling results in delay (and sometime lack) in implementation of newly-acquired safety information in generic drugs' labels	



2

MOVING IN DIFFERENT DIRECTIONS? A COMPARATIVE ANALYSIS OF THE GENERIC DRUG APPROVAL PROCESS IN DEVELOPED AND EMERGING MARKETS

The following section outlines the evolving regulatory approval framework NBCDs and NTI drugs in DRAs from a mixture of seven developed and emerging markets. It discusses what regulators and DRAs are doing in these individual markets. Key questions covered include: What are the current level of regulations for NTIs and NBCDs? Do they follow the 'one-size-fits all' approval pathway or are there special regulatory requirements in place for NTIs and NBCDs? Where are there still gaps?



2.1 The United States

Since the development of the ANDA pathway, the relative share of generic drugs approved by the FDA and on the US market has increased substantially, now accounting for approximately 80% of the American pharmaceutical market.⁷⁷ The ANDA pathway has also changed dramatically with continuous issuance of new guidance on regulatory and technical issues and updates.⁷⁸ However, with regards to the approval of generic NTI drugs and NBCDs the FDA is to some extent trailing other leading DRAs.

NTI drugs – gaps and challenges in existing practices

First, although several DRAs in developed countries such as Canada, Japan, Australia as well as international institutions such as the WHO have adopted recommendations for a narrower bioequivalence range of 90 to 111%/112% for NTI drugs, the FDA maintains the range of 80-125% for all generic drugs. A 2009 study by the then-acting director of the Division of Bioequivalence at the FDA found that this BE range is sufficient in determining bioequivalence en masse and that the approval process ensures the safety of generic substitution. The FDA's formal position documents state: "The FDA does not set specific standards

based on therapeutic index. The bioequivalence criteria... are quite strict; there is no need to apply stricter criteria for NTI drugs."⁷⁹

Still, in 2010 the FDA's Advisory Committee for Pharmaceutical Science and Clinical Pharmacology has agreed that the current BE standards are not sufficient for NTI drugs, and has suggested that the standards should be stricter.⁸⁰ The committee's recommendations for NTI drugs included a more rigorous trial design and a tighter BE range of 90%-111.1%.⁸¹ Following the Committee's recommendations the FDA has taken a research-based approach with regards to the regulatory gaps concerning NTI drugs.⁸² However, while several studies funded by the FDA have been published with recommendations (including an NTI definition, a narrower BE range and stricter BE trial design) these have only been partly implemented as draft guidance on a product-by-product basis.⁸³

Second, the FDA has developed a framework for a scientific, risk-based assessment of generic drug candidates' quality,⁸⁴ following the recognition that the current review system lacks the ability to effectively ensure product quality throughout the manufacturing process, particularly for complex drugs.⁸⁵ This regulatory approach, known as QbR, aims at ensuring that the generic product maintains its attributes under a controlled and appropriately designed manufacturing process.⁸⁶ The QbR approach recognizes generic NBCDs and NTI drugs as riskier drugs. As such,

TABLE 3 Key gaps in the regulatory framework for approval of follow-on versions of NTI drugs / NBCDs in the US

	Food & Drug Administration
Formal NTI definition	Under consideration
Required bioequivalence range for NTI drugs	80-125%
Specific requirements for BE trial design for NTI drugs	Under consideration
A list of NTI drugs is maintained and updated?	FDA recognizes some drugs as NTI drugs; NTI drugs list maintained in some states.
Generic substitution allowed for NTI drugs?	Determined on a state-level; forbidden by some
'Similarity' instead of 'equivalence' for follow-on versions of NBCDs?	No
Specific extended requirements for follow-on versions of NBCDs?	Partial, determined on a case-by-case basis
A stepwise approach and 'totality of evidence' requirement?	No
Automatic / generic substitution allowed for follow-on versions of NBCDs?	Yes

these NTI drug candidates necessitate a heavier emphasis by allocating more resources to their appraisal process and risk assessment.⁸⁷

However, the QbR approach does not accommodate, or compensate, for the sensitivities of NTI drugs and NBCDs, and discussed in the former sections. For example, while the FDA has published several guidance papers, such as for the NTI drug *Warfarin*, these are case-specific and not general rules or processes. What is more, for NBCDs the FDA has allocated funds for characterization and clinical comparison of innovative NBCDs and their follow-on versions, but only after these products were already approved for marketing within the US.⁸⁸

NBCDs – gaps and challenges in existing practices

Follow-on versions of NBCDs are currently approved under the conventional ANDA pathway.⁸⁹ For example, on several instances the FDA has commissioned research from external labs on

the safety and efficacy of follow-on versions of NBCDs, after these drugs were already approved for marketing.⁹⁰ In certain cases, such as with Low Molecular Weight Heparins, NBCDs are classified as biologic drugs by the EMA (and their follow-on versions are evaluated under the biosimilars pathway), but not by the FDA.⁹¹

The scientific challenges with this approach described above and increasing recognition that NBCDs require a special pathway has prompted action by American lawmakers. The *Generic Complex Drugs Safety and Effectiveness for Patients Act* law was introduced to the US Congress in March 2015. The bill would require the Government Accountability Office to assess the FDA's ability to adequately appraise and evaluate follow-on versions of NBCDs.⁹² The Office is also asked to assess whether the biosimilars approval pathway (section 505(j) of the *FD&C Act*) would be a more appropriate mechanism for the regulatory approval of follow-on versions of NBCDs.⁹³

In sum, there are substantial gaps in the FDA's regulatory approval process for generic versions of both NTI drugs and NBCDs. Opposite Table 3 provides a summary of the FDA's regulatory framework for these drugs.



2.2 The European Union

The EMA oversees the pharmaceutical market for the entire European Union. Although each EU-member state has its own DRA, the EMA maintains the centralized procedure, under which a drug candidate (either innovative or generic) can be approved for marketing for all EU member states. However, most generic drugs (including follow-on versions of NTI drugs and NBCDs) are submitted for approval via the decentralized or mutual recognition procedures.⁹⁴ Under these procedures, a drug candidate can gain marketing authorization in one EU member state based on the authorization given in another. Indeed, most generic companies submit their products for authorization under these procedures, especially after certain restrictions on naming and

TABLE 4 Key gaps in the regulatory framework for approval of follow-on versions of NTI drugs / NBCDs in the EU

	European Medicines Agency
Formal NTI definition	Yes
Required bioequivalence range for NTI drugs	90-111%, determined on a case-by-case basis
Specific requirements for BE trial design for NTI drugs	Fully replicated, 2-sequence, 2-treatment, 4-period crossover study design
A list of NTI drugs is maintained and updated?	No
Generic substitution allowed for NTI drugs?	Determined on a Member State-level; forbidden by some
'Similarity' instead of 'equivalence' for follow-on versions of NBCDs?	Determined on a case-by-case basis
Specific extended requirements for follow-on versions of NBCDs?	Determined on a case-by-case basis
A stepwise approach and 'totality of evidence' requirement?	Determined on a case-by-case basis
Automatic / generic substitution allowed for follow-on versions of NBCDs?	Yes

manufacturing variations were put in place under the centralized procedure.⁹⁵ This means that follow-on versions of NTI drugs or NBCDs can be granted marketing authorization in EU member states which maintain less stringent requirements and yet be authorized for use throughout the entire EU. For example, while a narrower BE range exist for generic NTI drugs in Switzerland and Spain, it does not in Romania and Greece.⁹⁶

NTI drugs – gaps and challenges in existing practices

While the EMA has adopted the requirement for a narrower BE range of 90-111% for NTI drugs in 2010 this is only on a case-by-case basis.⁹⁷ Moreover, the EMA does not maintain a list of NTI drugs.⁹⁸ While some countries, such as Belgium, maintain such a list, others, such as France, do not.⁹⁹ Critically, the lists also varies between countries.¹⁰⁰ For example, some drugs such as *Flecainide* and *Amiodarone* are considered being NTI drugs in Belgium, but not in other countries.¹⁰¹

Within this context, the generic substitution of NTI drugs constitute a potential pharmacovigilance gap (which EMA is responsible for), especially as generic substitution laws or guidelines varies in the freedom they provide for healthcare professional decisions. For example, strict substitution rules in the UK compel switching to a generic version once introduced, both for in-patients and out-patients, including NTI drugs such as immunosuppressants.¹⁰² In other member states, such as Italy, Spain and the Czech Republic, an automatic substitution to a generic version of an immunosuppressant is less likely as healthcare professionals tend to prefer the innovative treatment.¹⁰³ Overall, the commercial and regulatory incentives in place in a given market will have an impact both on the substitution policies in place but also, and this is critical, on the actual practices at the dispensation level. For example, are patients rigorously informed and made aware of the substitution of their medicines from one product to another? In many markets the manner in which policies are followed will vary from pharmacy to pharmacy.

NBCDs – gaps and challenges in existing practices

With respect to NBCDs the EMA is a relatively stringent drug regulator, as its practices are mostly in-line with the scientific recommendations discussed above in section 1, and efforts have been taken to further bolster and harmonize existing regulations. Most importantly, the EMA usually refers follow-on versions of NBCDs (though on a case-by-case basis) to the biosimilars pathway, which is deemed more rigorous and therefore appropriate for NBCDs. It is worth noting the contrast between EMA and FDA on these approvals. For example, EMA has refused to grant a marketing authorization for follow-on versions of NBCDs based on insufficient proof of safety and efficacy, while at the same time the FDA has approved the follow-on versions via the conventional generic approval model.¹⁰⁴

Nevertheless, in recent years several follow-on versions of NBCDs have been granted EU-wide marketing authorization via the decentralized or mutual recognition procedure. For example, five different versions of the NBCD Iron Sucrose are marketed in France today. In addition, one

TABLE 5 Key gaps in the regulatory framework for approval of follow-on versions of NTI drugs / NBCDs in Canada

	Health Canada
Formal NTI definition	Yes
Required bioequivalence range for NTI drugs	90-112%
Specific requirements for BE trial design for NTI drugs	Efforts for adequate representation of patient population and cover for potential risks
A list of NTI drugs is maintained and updated?	Yes
Generic substitution allowed for NTI drugs?	Determined on a regional level
'Similarity' instead of 'equivalence' for follow-on versions of NBCDs?	No
Specific extended requirements for follow-on versions of NBCDs?	No
A stepwise approach and 'totality of evidence' requirement?	No
Automatic / generic substitution allowed for follow-on versions of NBCDs?	Yes

such drug was recently approved for marketing in Sweden via the national procedure, despite the fact that the Swedish DRA had not based its decision on supportive clinical data; as is usual with biosimilars.¹⁰⁵

Despite the issuance of several "reflection papers" and "draft guidance" detailing the additional requirements for approval of follow-on versions of NBCDs, the regulatory framework for approval of these drugs is still lacking in the EU. This includes, for example: the absence of stricter requirements (such as stricter trial design), inability to stipulate generic substitution with 'totality of evidence', and the option for faster approval via decentralized procedures, constituting the most significant challenges from a pharmacovigilance perspective.



2.3 Canada and Australia

The Canadian DRA Health Canada is one of the world's leading DRAs and its practices are generally similar to that of the EMA and the FDA. Australia's drug regulator – the Therapeutic Goods Administration – is also considered a relatively advanced and stringent DRA. Generic drugs have a high market share in both countries. In regulatory terms, generic drug candidates undergo a similar regulatory process of market approval in both countries. Marketing authorization, however, is granted only for follow-on versions of drug already registered in Canada, and bioequivalence tests must be performed against this reference drug.¹⁰⁶

NTI drugs – gaps and challenges in existing practices

Health Canada was the world's first DRA to officially require a narrower range for NTI drugs (referred to as 'critical dose' drugs) in 2006.¹⁰⁷ In addition, Health Canada's guidance on BE trials recognizes that in certain cases involving generic NTI drug candidates it may be necessary to perform the BE trials on patients experiencing the targeted disease, rather than on healthy volunteers.¹⁰⁸ Moreover, Health Canada recognizes that study design is of critical importance for NTI drugs, and requires both fasting and fed states and homogenous study groups, among other requirements.¹⁰⁹

The Australian TGA also maintain similar definitions of what constitute an NTI drug and a requirement for a narrower BE range. However, the TGA does not refer to NTI drugs' BE trial design within its bioequivalence guidance and does not maintain a list of NTI drugs.¹¹⁰

Where the two DRAs significantly differ is in generic substitution. While the Australian TGA restricts generic substitution of certain NTI drugs such as *warfarin* and *phenytoin*,¹¹¹ in Canada, generic substitution by pharmacists is allowed, and even mandatory in several provinces, but it is not automatic and is rather subject to the prescribing physician's decision.¹¹² There are also

TABLE 6 Key gaps in the regulatory framework for approval of follow-on versions of NTI drugs / NBCDs in Australia

	Therapeutic Goods Administration
Formal NTI definition	Yes
Required bioequivalence range for NTI drugs	90-111%
Specific requirements for BE trial design for NTI drugs	No
A list of NTI drugs is maintained and updated?	No
Generic substitution allowed for NTI drugs?	No
'Similarity' instead of 'equivalence' for follow-on versions of NBCDs?	No
Specific extended requirements for follow-on versions of NBCDs?	No
A stepwise approach and 'totality of evidence' requirement?	No
Automatic / generic substitution allowed for follow-on versions of NBCDs?	Yes

potentially eligible for generic substitution without recommended monitoring over the subsequent drug's effect and safety.



2.4 Japan

Japan's generic drugs market share is relatively low, with only some 40% of total market volume in 2012.¹¹⁴ The Ministry of Health, Labor, and Welfare has developed a 5-year plan to increase generic drug use to over 60% by 2018.¹¹⁵

The regulatory framework for approval of generic drugs in Japan has been centralized in recent years following structural reforms. The Office of Generic Drugs, part of the Pharmaceuticals and Medical Devices Agency, is responsible for the evaluation of applications.¹¹⁶ However, the standards of practice (including bioequivalence parameters) are determined by the Japanese Institute of Health Sciences. The bioequivalence guidelines in use have not been updated since 2012.¹¹⁷ For this reason, one of the 5-year plans' targets is to "Establish guidelines for bioequivalence testing in order to respond to the increased complexity of bioequivalence assessments and the diverse pharmaceutical products that are being developed."¹¹⁸

NTI drugs – gaps and challenges in existing practices

Generic versions of NTI drugs must show proof of bioequivalence within a narrow range of 90-111%. Additionally, the Japanese DRA has issued the most comprehensive list of NTI drugs on the market, with close to 30 NTI drug products on it, including antiepileptic drugs, immune-suppressants, antidiabetic compounds and more.¹¹⁹ The Japanese authorities also impose more stringent requirements within NTI drugs' post-approval stage including manufacturing process and formulation changes.¹²⁰

Where the generic drugs' regulatory framework falls short is in the lack of requirements for stricter BE trial design for generic NTI drugs and the

some examples of NTI drugs being exempted from reimbursement substitution protocols in several provinces. For example, *Cyclosporine* was included in Quebec's drugs list as an NTI drug and it is exempt from Quebec's mandatory generic substitution plan.

NBCDs – gaps and challenges in existing practices

Currently, follow-on versions of NBCDs are appraised and approved for marketing both in Canada and in Australia under the conventional follow-on model despite both DRAs having established a designated pathway for biosimilars. In some cases, such as with low molecular weight heparins, Health Canada acts to clarify what is the appropriate regulatory pathway.¹¹³ From a pharmacovigilance perspective, this is a significant gap. It essentially means that follow-on versions of NBCDs can be authorized for marketing in these countries without a heightened proof of similarity. It also means that these products are

TABLE 7 Key gaps in the regulatory framework for approval of follow-on versions of NTI drugs / NBCDs in Japan

	Pharmaceuticals and Medical Devices Agency
Formal NTI definition	Yes
Required bioequivalence range for NTI drugs	90-111%
Specific requirements for BE trial design for NTI drugs	No
A list of NTI drugs is maintained and updated?	Yes
Generic substitution allowed for NTI drugs?	Yes
'Similarity' instead of 'equivalence' for follow-on versions of NBCDs?	No
Specific extended requirements for follow-on versions of NBCDs?	No
A stepwise approach and 'totality of evidence' requirement?	No
Automatic / generic substitution allowed for follow-on versions of NBCDs?	Yes

practice of generic substitution. For example, generic substitution in Japan is permitted only with the approval of the attending physician. Up to 2008 the prescription format required the physician's signature for substitution. In an effort to increase generic market share, the format was changed into a tick-box that the physician is required to check for "no substitution".¹²¹

NBCDs – gaps and challenges in existing practices

Although a designated pathway for biosimilars is in place follow-on versions of NBCDs are appraised and approved for marketing under the conventional generic follow on product route.



2.5 Mexico

The Mexican generic drugs market has flourished during recent years, following extensive reform by the Mexican DRA COFEPRIS.¹²² For example, in late 2013 the regulation for establishing interchangeability (NOM-177-SSA1-2013) was introduced and was bolstered with additional requirements such as specific requirements for various types of drugs including a narrower BE range for NTI drugs.¹²³

NTI drugs – gaps and challenges in existing practices

With the introduction of NOM-177-SSA1-2013 several gaps with regards to NTI drugs were closed. In particular, the requirement for a narrower BE range of 90-111%, stricter protocols for BE studies and extension of dissolution profiles provides a more rigorous approach, in-line with scientific recommendations and international best practices.

Where Mexico's updated and more rigorous regulatory framework does not meet the most up-to-date recommendations and best practices for generic NTI drugs is in interchangeability and substitution policies. Indeed, NOM-177-SSA1-2013 states that generic drugs which exhibit sufficient proof of pharmaceutical and bioequivalence are interchangeable. Furthermore, prescribing by INN is mandatory in Mexico for public health system prescriptions. Private sector insurance and formularies do not mandate INN prescribing and instead prescribers can prescribe by brand name.¹²⁴

NBCDs – gaps and challenges in existing practices

Despite having a biosimilars pathway in place NBCDs are not required to undergo additional regulatory scrutiny but are processed under the conventional generic market authorization route.

Current Mexican regulations on interchangeability does not include any reference to NBCDs.

TABLE 8 Key gaps in the regulatory framework for approval of follow-on versions of NTI drugs / NBCDs in Mexico

	Comisión Federal para la Protección contra Riesgos Sanitarios
Formal NTI definition	No
Required bioequivalence range for NTI drugs	90-111%
Specific requirements for BE trial design for NTI drugs	No
A list of NTI drugs is maintained and updated?	No
Generic substitution allowed for NTI drugs?	Yes
'Similarity' instead of 'equivalence' for follow-on versions of NBCDs?	No
Specific extended requirements for follow-on versions of NBCDs?	No
A stepwise approach and 'totality of evidence' requirement?	No
Automatic / generic substitution allowed for follow-on versions of NBCDs?	Yes

Drug and Reference Drug Product. Since the early and mid-2000s Brazil has introduced measures to effectively curtail the use and distribution of similars, replacing them with bioequivalent tested generic drugs. Regulations introduced in 2003 require all similar drugs to submit bioavailability data, pharmaceutical equivalence tests and a copy of GMP certificate issued by the national DRA, ANVISA. However the more stringent regulations for similars has been watered down on several occasions and postponed (including in 2009). 2014 saw the regulation regarding similars updated (Resolution RDC No. 56/2014) and manufacturers of similars were given a period of time for submitting bioequivalence studies.¹²⁶ These regulations stipulate that following approval a similar will be regarded as 'equivalent' to a reference product and therefore interchangeable with the reference drug, just like generic medicines. Given the large market share of similars on the Brazilian market – and reliance by the public health system on these drugs – at the time of research it remained unclear whether manufacturers of similar drugs that will not abide with this requirement will still be permitted to distribute their product. It is also unclear whether these products can continue to be distributed with an exact copy of the reference product's safety information and leaflet as was permitted by ANVISA before the new regulation.¹²⁷



2.6 Brazil

Brazilian pharmaceutical policy has traditionally been committed to non-research based medicines. Historically this was achieved through the promotion of a copied-drugs industry built during the 1980s. These drugs are today known as similars or similares and constitute a substantial share of the Brazilian drug market. Brazil is one of the biggest markets for similar drugs in Latin America, with a market share of nearly 50%. In contrast, innovative and generic drugs have a market share of only 21% and 27% respectively.¹²⁵ Indeed, as in other Latin American countries including Argentina, there is currently a regulatory distinction between 3 different types of pharmaceuticals: Similar Drug Product, Generic

With respect to the conventional process of generic drugs approval, Brazil's requirements are largely the same as in other jurisdictions. Some key differences include additional requirements which are in-line with scientific recommendations, such as: proportionality between male and female subjects; maintaining an average of body weight; and studies where food interaction are known.¹²⁸

NTI drugs – gaps and challenges in existing practices

NTI drugs are not mentioned specifically in current bioequivalence standards nor is there a list of recognized NTI drugs. Furthermore, following Resolution RDC No. 56/2014 the list of interchangeable drugs has increased substantially with drugs whose bioequivalence is proven but under the conventional generic follow-on route. While ANVISA does specify the requirements for BE studies for specific types of drugs such as highly

TABLE 9 Key gaps in the regulatory framework for approval of follow-on versions of NTI drugs / NBCDs in Brazil

	ANVISA
Formal NTI definition	No
Required bioequivalence range for NTI drugs	80-125%
Specific requirements for BE trial design for NTI drugs	No
A list of NTI drugs is maintained and updated?	No
Generic substitution allowed for NTI drugs?	Yes
'Similarity' instead of 'equivalence' for follow-on versions of NBCDs?	No
Specific extended requirements for follow-on versions of NBCDs?	No
A stepwise approach and 'totality of evidence' requirement?	No
Automatic / generic substitution allowed for follow-on versions of NBCDs?	Yes

variable drugs and modified-release drugs, no specifications exist for NTI drugs.¹²⁹

Highlighting the need for regulatory reform a number of local academic papers have emphasized the pressing need for bolstering the regulations regarding generic version of marketed NTI drugs, such as *Levothyroxine*.¹³⁰ It remains to be seen whether these recommendations will be adopted.

NBCDs – gaps and challenges in existing practices

To date, ANVISA has not established a designated pathway for NBCDs, or added specific requirements for the appraisal of their follow-on versions.¹³¹

Yet just as with NTIs this is an issue which is recognized by experts in Brazil and the wider region. For instance, a 2015 panel of Latin American experts from nine countries (including Brazil) provided recommendations on biosimilars

and on follow-on versions of NBCDs. Among their recommendations was: the need to have a robust regulatory framework based on up-to-date standards of manufacturing and pharmacovigilance prior to market approval; the need for full characterization of the products; and restriction on automatic substitution due to "unacceptable risks to patients".¹³²

Summary

This section has provided a comparative analysis of the current practices for generic drug approval within a mixture of seven developed and emerging markets, focusing on NTI drugs and NBCDs.

The analysis shows, first, that gaps and challenges exist to an extent in all examined DRAs, including stringent DRAs such as FDA, EMA, Health Canada, PMDA and the TGA. Second, it is clear that this is not an issue facing only DRAs in emerging markets. In fact, the FDA and the US – despite recognizing these issues – have yet to introduce reforms and strengthen regulatory requirements for NTIs and NBCDs.

On the following page Table 10 consolidates the current practices of the seven analyzed DRAs showing where best practices are in place and where there is still room for improvement.

TABLE 10 Key gaps in the regulatory framework for approval of follow-on versions of NTI drugs / NBCDs in seven developed and emerging markets

	United States (FDA)	European Union (EMA)	Canada (Health Canada)	Australia (TGA)	Japan (PMDA)	Mexico (COFEPRIS)	Brazil (ANVISA)
Formal NTI definition	Under consideration	Yes	Yes	Yes	Yes	No	No
Required bioequivalence range for NTI drugs	80-125%	90-111%, determined on a case-by-case basis	90-112%	90-111%	90-111%	90-111%	80-125%
Specific requirements for BE trial design for NTI drugs	Under consideration	Fully replicated, 2-sequence, 2-treatment, 4-period crossover study design	Efforts for adequate representation of patient population and cover for potential risks	No	No	No	No
A list of NTI drugs is maintained and updated?	FDA recognizes some drugs as NTI drugs; NTI drugs list maintained in some states.	No	Yes	No	Yes	No	No
Generic substitution allowed for NTI drugs?	Determined on a state-level; forbidden by some	Determined on a state-level; forbidden by some	Determined on a regional level	No	Yes	Yes	Yes
'Similarity' instead of 'equivalence' for follow-on versions of NBCDs?	No	Determined on a case-by-case basis	No	No	No	No	No
Specific extended requirements for follow-on versions of NBCDs?	Partial, determined on a case-by-case basis	Determined on a case-by-case basis	No	No	No	No	No
A stepwise approach and 'totality of evidence' requirement?	No	Determined on a case-by-case basis	No	No	No	No	No
Automatic / generic substitution allowed for follow-on versions of NBCDs?	Yes	Yes	Yes	Yes	Yes	Yes	Yes



3

KEY FINDINGS AND CONCLUSIONS

Increasingly scientists and drug regulators across the world are recognizing the need to depart from the traditional 'one-size-fits-all' generic approval framework and establish additional pathways for NTI drugs and NBCDs.

Scientific research from North America, Europe and Latin America show the need for a tightening of regulatory standards for NTIs, NBCDs and other high risk follow-on products. And while some DRAs have taken action introducing a narrower bioequivalence band, for instance, for NTIs the regulatory standards and practices for the appraisal of follow-on versions of NTI drugs and NBCDs are currently lagging behind the recommendations and findings of the latest scientific research.

Indeed, while most DRAs included in this report recognize the higher risks that these drugs pose, actual regulatory standards and requirements vary greatly between drug regulators. Some DRAs have introduced more stringent, rigorous requirements specific to generic versions of these drugs; others have not. In fact, follow-on versions of NTI drugs and NBCDs are authorized for marketing in many countries under the conventional generic pathway. This despite scientific recommendations largely being unanimous for the need for specific conditions and pathways for these drugs and despite a large body of evidence indicating the associated potential health and safety risks. Furthermore, definitions as to what constitutes these higher risk follow-on products and more complex drugs is not uniform. Lists of NTI drugs can differ considerably between the few drug regulators that maintain them as well as within countries – such as in the US – and between different layers of authority. And in some countries, particularly in Latin America, the challenges posed by these drugs is compounded by the existence of a third class of drugs – *similares* – which are sold as follow-on versions of the innovative product, yet without the need to provide proof bioequivalence.

The report's findings can be grouped along three key findings:

Key finding 1: NTI drugs and NBCDs necessitate a more rigorous regulatory approach

A growing body of scientific evidence now clearly indicates that the conventional, 'one-size-fits-all' approach in the regulatory approval of generic drugs is technically inadequate for ensuring the safe and effective use of follow-on versions to the reference product, especially with regards to NTIs and NBCDs.

With respect to NTI drugs, evidence suggests that small, seemingly insignificant changes to the drug's formulation, compound or excipients, undetected or unaccounted for by the current regulatory approval model, may, and indeed already have resulted in poorer efficacy and a wide range of adverse reactions, toxicity and unwarranted clinical outcomes. These concerns are compounded by the practice of generic substitution which exists in many countries today, yet often fails to address the health and safety challenges posed by generic versions of NTI drugs.

With respect to NBCDs, experts from across the board agree that the current analytical methods which are utilized for the appraisal of follow-on versions are incapable of full characterization of complex drugs and therefore cannot safely establish equivalence and interchangeability between an innovative complex drug and its follow-on versions. Thus, follow-on versions of complex drugs can only be deemed as 'similar' and not equivalent.

To ensure that generic versions of NTI drugs and NBCDs maintain the same safety, quality and efficacy properties of the reference product, scientific recommendations include the following:

NTI drugs

- A narrower range of 90-111% for determining bioequivalence, instead of the general 80-125%;
- Stricter bioequivalence trial design which ensures that the difference between the reference and follow-on products are negligible under the acceptable statistical validity;
- Maintaining a list of NTI drugs;
- Permit generic substitution of NTI drugs only under the conditions of switching in a highly-controlled manner, and with appropriate therapeutic monitoring for adverse drug reactions and toxicity.

NBCDs

- Follow-on versions of non-biological complex drugs should be appraised under the stepwise approach of the biosimilars pathway, where the follow-on product is developed through an iterative development to fit the process as similar as possible to that of the reference product, and its similarity is determined using a 'totality of evidence' which involves the state-of-the-art analytical methods as well as clinical studies;
- The follow-on version's interchangeability may only be established throughout the product's life-cycle, due to the sensitivity of the production process. As a result, generic substitution is discouraged or not recommended without the monitoring of a healthcare professional.

Key finding 2: DRAs have been slow in addressing the challenges posed by NTI drugs and NBCDs and patients potentially remain at risk

This report's mapping of the current practices for generic drug approvals for NTI drugs and NBCDs in seven developed and developing markets confirms that the 'one-size-fits-all' approach suffers from substantial gaps with respect to the current

state of the scientific literature. Indeed, among the seven examined drug regulators (which include both stringent as well as developing DRAs) none has implemented in full (or even in part, in some cases) the recommended standards and practices for approving follow-on versions of NTI drugs and NBCDs.

For NTIs there has been some positive movement with five of the seven DRAs mapped introducing narrower bioequivalence bands of 90-112% for NTIs. Yet significant gaps still remain.

Conversely, for NBCDs no DRA has changed regulatory requirements and procedures for these follow-on products.

Interestingly, where these gaps and challenges are most striking is within the most stringent and advanced DRAs, namely the FDA and the EMA.

In the US NTI drugs still lack a formal definition, a federal-level list, and, most importantly, a narrower range of bioequivalence. While some generic versions of NTI drugs may and have been asked to undergo a stricter bioequivalence trial, this is determined only on a case-by-case basis. The *Generic Complex Drugs Safety and Effectiveness for Patients Act* was introduced to the US Congress in March 2015. The bill would require the Government Accountability Office to assess the FDA's ability to adequately appraise and evaluate follow-on versions of NBCDs. The bill also asks the Office to assess whether the biosimilars approval pathway (section 505(j) of the FD&C Act) would be a more appropriate mechanism for the regulatory approval of follow-on versions of NBCDs. While this proposed legislation is being debated the FDA has allocated funds for research into the equivalence of follow-on versions of NBCDs that are already marketed, and to which compendial monographs are still in development.

In the EU, generic drugs manufacturers are increasingly using the decentralized procedures for approving their products. Thus, while the EMA itself maintain stricter requirements for approval of follow-on versions of NTI drugs and NBCDs, follow-on products can be authorized for marketing in one Member State with less-strict regulations, and gain access to the entire EU market via the mutual recognition procedure.

Key finding 3: Regulatory convergence is taking place – Next step should include NTIs and NBCDs

The regulatory approval process for generic drugs – which includes standards governing bioequivalence and labeling to manufacturing and dispensation – is in most major respects converging. Since the mid-1980s and passage of the Hatch-Waxman Act in the US, most major DRAs have introduced similar pathways for follow-on products. Generic drugs are required to provide bioequivalence data that underpin the assumptions about pharmaceutical and therapeutic equivalence between reference and follow-on product and their safe and effective use. Even in countries like Brazil with a strong tradition and use of copied drugs (*similares*) reforms have been introduced to increase the number of bioequivalent tested products on the market.

As mentioned, five of the seven DRAs examined in this report have taken partial measures strengthening regulatory requirements for NTIs. The WHO and other international institutions are also working on improving best practices for the approval of generic follow-on products. Once a growing body of DRAs introduce reforms to both the approval process for NTIs and NBCDs there is a good chance this can become an established international best practice and regulatory convergence is more likely to take place.



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