

Regulatory Science of Complex Generics: Q3 Characterization and Bioequivalence

Ms. Rahiba K V¹, Ms. Hridhya M², Mr. Mohamed Shameer Kp³,
Ms. Sona Fathima S⁴, Ms. V A Anshila⁵

^{1,2,3,4,5}Student, Pharmaceutics, Alshifa College Of Pharmacy

Abstract

Complex generic drug products occupy an increasingly important space between conventional small-molecule generics and highly complex biological medicines [1,2]. Their equivalence cannot always be demonstrated adequately by a simple comparison of active ingredient content and systemic exposure because formulation structure, microarchitecture, drug distribution, release behavior, and manufacturing history may materially influence performance [1,2]. This review examines a regulatory-science framework that links qualitative and quantitative composition (Q1/Q2), physicochemical and structural characterization (Q3), in-vitro performance, and bioequivalence evidence for complex generics [3,4]. Particular attention is given to topical semisolids, long-acting injectable products, liposomal and other non-biological complex drugs, because these classes illustrate different mechanisms by which formulation and process variables can affect critical quality attributes and clinical performance [5–8]. Recent regulatory developments are considered alongside scientific literature, with emphasis on the evolving use of comparative Q3 characterization, in-vitro release testing, in-vitro permeation testing, pharmacokinetic approaches, and model-informed evidence [9–12]. The review also considers Quality by Design as a framework for linking material attributes and process parameters to critical quality attributes and regulatory control strategies [13,14]. A comparative perspective on the United States and European regulatory environments highlights areas of convergence as well as remaining differences in evidentiary expectations [15,16]. The review proposes an integrated, risk-based evidence model in which no single analytical test is assumed to establish equivalence for every complex product [1,2]. Instead, orthogonal characterization and performance data should be combined according to the product's mechanism, route of administration, critical quality attributes, and residual uncertainty [1,2]. Such an approach may improve scientific consistency, reduce unnecessary clinical burden, and support development of high-quality generic alternatives [1,2].

Keywords: complex generics; bioequivalence; Q3 characterization; critical quality attributes; in-vitro release; in-vitro permeation; regulatory science; Quality by Design; non-biological complex drugs.

1. Introduction

Generic medicines are expected to provide the same therapeutic benefit as their reference products while reducing development costs and improving access to treatment [17]. For conventional immediate-release small-molecule products, equivalence can often be established using well-established concepts of pharmaceutical equivalence, dissolution testing, and pharmacokinetic bioequivalence [18]. The situation becomes substantially more complicated when the product contains a complex formulation, a complex

active substance, a locally acting route, or a dosage form in which the manufacturing process creates an important performance-defining structure [1,19]. Such products are commonly described as complex generics, although terminology differs between regulatory jurisdictions and scientific communities [2,20]. The regulatory importance of complex generics has increased because many products approaching loss of exclusivity are technically difficult to reproduce, creating barriers to competition even when conventional patent protection has expired [6,21]. Examples include long-acting injectables, liposomes, nanoparticle-based formulations, complex topical products, inhalation products, and other modified-release or locally acting systems [5,7,22]. In these products, the identity and amount of the active pharmaceutical ingredient are necessary but may be insufficient descriptors of sameness [1,17]. Particle-size distribution, internal microstructure, surface characteristics, phase behavior, rheology, drug partitioning, encapsulation, release kinetics, and manufacturing history can influence the final product performance [8,13,23]. The concept of Q3 characterization has therefore gained importance, particularly for topical semisolid products [1,17]. Q3 describes physicochemical and structural attributes that arise from the formulation and manufacturing process and that may influence drug availability at the site of action [3,24]. Recent regulatory developments have moved toward a more structured characterization of these attributes, while scientific studies increasingly investigate their relationship with in-vitro release, permeation, and bioequivalence [9,10,25]. The resulting regulatory-science question is not simply whether a generic product has the same ingredients, but whether the test product reproduces the relevant quality and performance characteristics of the reference product to a degree that supports equivalent clinical performance [1,17]. This review critically examines that question [1,17]. It integrates pharmaceutical development principles with regulatory evidence requirements and proposes a product-centered framework for selecting characterization and equivalence tools [1,17]. Rather than treating Q3 characterization as a stand-alone analytical exercise, the review considers Q3 as part of an evidence chain connecting formulation composition and process variables with critical quality attributes, in-vitro performance, pharmacokinetics, and, where necessary, clinical or pharmacodynamic evidence [12,14].

2. Literature Search and Review Approach

A narrative regulatory-science review approach was used to identify peer-reviewed literature relevant to complex generic drug development, pharmaceutical equivalence, Q3 characterization, in-vitro performance testing, bioequivalence, and regulatory assessment [1,2]. Literature published primarily between 2014 and 2026 was prioritized, while earlier foundational publications were retained when they established concepts still used in current regulatory science [1,2]. Searches were structured around combinations of terms including “complex generic,” “non-biological complex drug,” “Q3 characterization,” “topical generic,” “bioequivalence,” “in-vitro release,” “in-vitro permeation,” “long-acting injectable,” “liposome,” “quality by design,” and “regulatory science.” Peer-reviewed articles from internationally recognized pharmaceutical, biopharmaceutics, drug-delivery, and regulatory-science journals were prioritized [1,2]. Current FDA and EMA regulatory documents were used to contextualize the scientific literature because guidance documents provide the most direct description of contemporary regulatory expectations [3,15,16]. The review is intentionally critical rather than purely descriptive: evidence-generation approaches are compared according to their scientific rationale, sensitivity to formulation differences, translational value, and potential regulatory utility [1,2].

3. Complex Generic Drug Products: Definition and Sources of Complexity

The term complex generic does not represent a single dosage form or a universally harmonized regulatory category [1,2]. In the United States, the FDA has described complex products using several dimensions, including complex active ingredients, complex formulations, complex routes of delivery, complex dosage forms, and certain drug-device combinations [1,19]. The concept of non-biological complex drugs (NBCDs) provides a complementary scientific perspective for products in which the active substance or delivery system consists of closely related structures that cannot be fully described by conventional physicochemical characterization alone [2,26]. Although these definitions overlap, they are not interchangeable [1,2]. A product can be complex because of its formulation or route even when its active molecule is chemically simple, whereas an NBCD may be intrinsically complex at the active-substance level [20]. From a pharmaceutical perspective, complexity matters when a measurable property of the product is linked to clinical performance and is difficult to reproduce by conventional generic-development methods [7]. A conventional tablet may tolerate modest differences in excipient grade or manufacturing history when dissolution and bioequivalence remain within established limits [1,2]. By contrast, a liposome can exhibit changes in size, lamellarity, lipid composition, drug-to-lipid ratio, surface characteristics, or encapsulation state that alter distribution and release without changing the nominal dose [5,27]. Similarly, a long-acting injectable can show substantial changes in release behavior as a consequence of polymer molecular weight, particle size, porosity, drug loading, depot formation, or injection-site behavior [6,28]. Topical semisolids illustrate another form of complexity [1,2]. The same nominal concentration of an active ingredient can be incorporated into different microstructures, including emulsions, gels, suspensions, and multiphase systems [1,2]. Droplet or particle size, rheological behavior, thermodynamic activity, polymorphic state, solvent composition, and drug partitioning can alter release and skin penetration [24,29]. Moreover, topical products can undergo “metamorphosis” after application as water or volatile components evaporate and the formulation becomes more concentrated or structurally different [30]. Consequently, a laboratory characterization performed only on the packaged product may not fully represent the product state during use [1,2]. The regulatory consequence is that pharmaceutical equivalence must be interpreted in relation to the product’s mechanism of action and route of administration [1,2]. The more strongly performance depends on structure, the greater the need for orthogonal characterization and functional testing [13,31]. A useful development strategy therefore begins by identifying the product attributes that plausibly connect composition and process to performance [1,2]. These attributes become candidate critical quality attributes and provide the basis for a rational equivalence strategy [1,2]. The distinction between complexity and novelty is also important [1,2]. A complex generic does not necessarily need a novel analytical technique; rather, it requires a sufficiently sensitive and scientifically justified package of evidence [1,2]. In some cases, established techniques such as particle-size analysis, microscopy, rheology, dissolution, or chromatography may be more informative than a sophisticated but poorly validated method [14,32]. Regulatory science should therefore emphasize fitness for purpose, method discrimination, reproducibility, and linkage to product performance rather than technological sophistication alone [1,2].

Table 1 [1,2]. Major sources of complexity and potentially relevant equivalence evidence [1,2]

Product class	Key complexity	Important CQAs/Q3 attributes	Potential equivalence evidence
Topical semisolids	Multiphase microstructure; local action	Rheology, globule/particle size, pH, polymorph, drug activity	Q1/Q2/Q3, IVRT, IVPT, dermatopharmacokinetics
Long-acting injectables	Depot formation and prolonged release	Particle size, polymer attributes, drug loading, release kinetics	Physicochemical characterization, IVRT, PK/BE, IVIVC
Liposomes/NBCDs	Structured carrier and process-dependent properties	Size/PDI, morphology, lipid composition, encapsulation, release	Orthogonal CMC characterization, comparative PK, functional assays
Modified-release oral products	Release mechanism and dosage-form architecture	Dissolution profile, coating/matrix attributes, mechanical properties	Comparative dissolution, BE, IVIVC/biowaiver where justified
Complex inhalation products	Device-formulation interaction and aerodynamic behavior	Particle-size distribution, emitted dose, aerodynamic size	In-vitro performance, device characterization, PK/PD/clinical evidence

4. From Q1/Q2 Sameness to Q3 Characterization

The traditional generic-development paradigm emphasizes qualitative composition (Q1) and quantitative composition (Q2) as major elements of pharmaceutical sameness [24]. For many conventional dosage forms, Q1/Q2 information combined with appropriate manufacturing controls can provide a strong basis for predicting comparable product performance [3,24]. However, complex formulations can exhibit different physical structures despite similar composition, and these differences may influence drug release, distribution, stability, or local availability [8,23]. Q3 characterization addresses this gap by describing the physicochemical and structural state of the drug product [3,24]. In topical formulations, relevant Q3 attributes may include pH, viscosity, rheological profile, globule or particle size, polymorphic form, drug state, water activity, phase behavior, and other microstructural characteristics [3,24]. The central scientific rationale is that Q3 attributes act as intermediate variables between Q1/Q2 composition and clinical performance [3,24]. They are therefore useful when they can be shown to be sensitive to formulation differences and mechanistically related to product performance [31]. The value of Q3 characterization depends on method selection [3,24]. Microscopy can reveal particle or droplet structure, but image interpretation and sampling can introduce variability [3,24]. Laser diffraction provides quantitative particle-size distributions but may not describe the complete microstructure of a semisolid [3,24]. Rheology can be highly sensitive to changes in internal structure, yet the result depends on geometry, shear history, temperature, and method parameters [32,33]. Spectroscopic techniques can provide chemical-state information, while thermal analysis can detect transitions and changes in physical

state [3,24]. No single method is likely to capture all relevant dimensions of a complex formulation [3,24]. The concept of a “structural fingerprint” is useful for understanding this multidimensionality [3,24]. A fingerprint is not simply a long list of analytical results; it is a predefined set of attributes selected because they are plausibly related to product performance [14]. Such an approach reduces the risk of generating large volumes of descriptive data without knowing which differences matter [3,24]. It also supports regulatory communication because the applicant can explain why each attribute is included, how it is measured, and what acceptance or comparison criterion is scientifically justified [3,24]. Q3 characterization should also be linked to manufacturing process understanding [3,24]. Two products can have identical target compositions but different microstructures because of differences in mixing energy, order of addition, temperature history, homogenization, milling, drying, or sterilization [23,34]. Consequently, Q3 characterization can serve as a bridge between formulation development and process validation [3,24]. If a process parameter has a demonstrated effect on a critical Q3 attribute, the parameter becomes part of the control strategy rather than an isolated manufacturing detail [3,24]. The regulatory significance of this concept is particularly evident in topical generics [3,24]. The FDA’s final 2026 Q3 guidance describes basic and comprehensive Q3 characterization as tools for identifying dosage-form structure and describing attributes that may be critical to performance [3]. The guidance also distinguishes between Q3 sameness, similarity, and difference, reflecting the principle that the regulatory consequence of a formulation difference depends on whether that difference is likely to affect performance [3]. This is an important evolution from a purely compositional view of generic sameness toward a performance-informed assessment [3,24].

5. In-Vitro Performance as a Bridge Between Quality and Bioequivalence

In-vitro performance testing becomes particularly valuable when a complex product acts locally, releases drug over an extended period, or contains a structure that cannot be adequately represented by systemic pharmacokinetic measurements alone [4,35]. The principal advantage of an in-vitro test is that it can directly interrogate a product attribute that is expected to influence performance while avoiding some of the variability and ethical burden associated with human studies [9]. For topical products, in-vitro release testing (IVRT) measures the rate at which drug is released from the formulation through a synthetic membrane into a receptor phase [4,36]. IVRT is sensitive to formulation variables such as drug solubility, particle size, vehicle composition, viscosity, and thermodynamic activity, making it useful for formulation development, scale-up, batch comparison, and certain regulatory submissions [24,36]. However, IVRT does not reproduce the skin barrier and therefore should not automatically be interpreted as a direct measure of cutaneous absorption [9,36]. Its strongest role is often as a discriminating product-performance test that complements other evidence [10]. In-vitro permeation testing (IVPT) uses biological skin membranes and can provide information about drug deposition and permeation across the skin [37]. Its physiological relevance is greater than that of IVRT, but variability in skin source, donor characteristics, integrity, thickness, storage, receptor conditions, and experimental design can influence results [37,38]. The measurement of mass balance is particularly important because drug retained within the skin may be pharmacologically relevant for locally acting products even when little drug appears in the receptor compartment [37]. The statistical treatment of in-vitro performance data is also a regulatory issue [9,36]. Similarity should not be declared simply because mean curves appear visually close [9,36]. The method must have adequate discriminatory ability, validated precision, appropriate sampling intervals, and predefined acceptance criteria [4,36]. Equivalence metrics should be

selected in relation to the mechanism of the product and the purpose of the test [9,36]. A release test that cannot detect meaningful formulation changes has limited regulatory value, even if its analytical precision is excellent [9,36]. Recent technological developments illustrate the direction of the field [9,36]. Stimulated Raman scattering microscopy has been investigated for mapping drug distribution in skin and assessing cutaneous bioequivalence, demonstrating how spatially resolved analytical techniques may supplement conventional release and permeation studies [11]. Raman spectroscopy has also been explored for extracting cutaneous pharmacokinetic information from topical products, with potential implications for reducing reliance on large clinical endpoint studies [12]. These techniques are promising because they attempt to connect pharmaceutical performance more directly with the location and temporal behavior of the active ingredient [9,36]. The same principle applies to long-acting injectables [9,36]. In-vitro release testing can characterize release kinetics over weeks or months, but the challenge is to demonstrate that the selected in-vitro method is predictive of in-vivo performance [6,39]. Factors such as polymer degradation, depot geometry, particle agglomeration, injection volume, tissue environment, and local clearance can make a simple dissolution-style test insufficient [9,36]. Development of clinically relevant IVIVC or mechanistic in-vitro/in-vivo relationships is therefore an important research need [28,40].

Table 2 [9,36]. Comparison of major equivalence tools for complex generic products [9,36]

Tool	Primary information	Main strength	Major limitation	Regulatory role
Q1/Q2	Composition and concentrations	Simple, reproducible comparison	May not capture microstructure	Foundational sameness evidence
Q3 characterization	Physicochemical/structural state	Mechanistically informative	Multidimensional; acceptance criteria may be product-specific	Supports pharmaceutical equivalence/BE strategy
IVRT	Drug release from formulation	Sensitive to formulation differences	Does not reproduce biological barrier	Performance comparison, development, selected BE pathways
IVPT	Skin permeation/deposition	Greater physiological relevance	High biological variability	Supports topical BE/equivalence
PK/BE	Systemic exposure	Direct clinical exposure measure	May miss local differences; resource intensive	Core evidence when applicable
IVIVC/PK modeling	Link between in-vitro and in-vivo behavior	Can reduce uncertainty and guide development	Requires robust mechanistic validation	Model-informed support where justified

6. Bioequivalence Assessment of Complex Generics

Bioequivalence is fundamentally a question of whether two products can be expected to produce equivalent exposure or effect under specified conditions [17]. The appropriate evidence depends on the route of administration, site of action, mechanism of release, and relationship between product characteristics and clinical outcome [18]. Applying a single conventional BE model to every complex generic can therefore create either unnecessary development burden or insufficient sensitivity to meaningful differences [4,17]. Topical products provide the clearest example [4,17]. For locally acting topical medicines, plasma concentrations may be low or poorly correlated with local effect, making conventional systemic PK unsuitable as the sole measure of equivalence [9,25]. Historically, clinical endpoint studies have therefore been used, but such trials can be expensive, time-consuming, and statistically inefficient because variability in disease severity and application behavior can obscure formulation-related differences [4]. Regulatory science has consequently moved toward modular approaches in which pharmaceutical characterization, IVRT, IVPT, dermatopharmacokinetics, pharmacodynamic methods, and clinical evidence can be combined according to the product [4,25]. The modular concept is important because it shifts the question from “Which single BE study should be performed?” to “What combination of evidence most directly addresses the residual uncertainty?” [41]. For example, a topical product that demonstrates Q1/Q2 sameness and strong Q3 similarity may require less additional evidence than a product with a meaningful microstructural difference [4,17]. Conversely, a product with identical composition but a different manufacturing process may require performance testing if the process can alter Q3 attributes [3,34]. For NBCDs and liposomal products, the situation is even more complex [4,17]. Conventional measures of total drug exposure may not distinguish free drug from encapsulated drug, even though the two fractions can have different pharmacological behavior [5,27]. Comparative characterization may therefore include particle-size distribution, lipid composition, encapsulation efficiency, drug leakage, morphology, surface characteristics, release behavior, and other product-specific attributes [5,7]. Some regulatory pathways additionally require comparative pharmacokinetic studies or functional assays depending on the product and reference standard [2]. Long-acting injectable products present another challenge because the relevant endpoint is not only the amount absorbed but the temporal pattern of release [6]. Two products can produce similar overall exposure while differing in early release, late release, or duration of effect [4,17]. Conversely, differences in in-vitro release may not necessarily translate into clinically meaningful differences if the system has compensatory mechanisms in vivo [28,39]. This creates a need for carefully designed release methods and, where possible, validated IVIVC or mechanistic understanding [4,17]. Bioequivalence therefore should be understood as an evidence hierarchy rather than a single experiment [4,17]. The foundation is product understanding; Q1/Q2 and Q3 data establish pharmaceutical similarity; functional in-vitro testing evaluates performance; PK, PD, or clinical studies are used when residual uncertainty cannot be adequately resolved by the preceding layers [14,31]. The strength of the overall conclusion depends on the coherence of these evidence streams rather than on the quantity of individual tests [4,17].

7. United States and European Regulatory Perspectives

The United States and European regulatory systems share the objective of ensuring that generic products provide equivalent quality and therapeutic performance, but their implementation for complex products is not completely harmonized [15,16,42]. The FDA has developed a dedicated complex-generics program and has issued product-specific guidances and general recommendations addressing selected

complex products [1,3]. The European framework more frequently uses general scientific guidelines, hybrid application pathways, and product-specific scientific advice, particularly for products that do not fit the conventional generic model [2,20]. For topical products, the FDA has progressively expanded characterization-based approaches [2,15]. Its 2026 final guidance on Q3 characterization provides recommendations for basic and comprehensive physicochemical and structural characterization of topical products submitted in ANDAs [3]. The agency's approach recognizes that Q3 differences can affect the level and type of additional BE evidence required [2,15]. The FDA has also developed guidance concerning IVRT and IVPT, reflecting an effort to establish standardized, scientifically justified alternatives to clinical endpoint studies [36,43]. The EMA has developed a guideline on the quality and equivalence of locally applied, locally acting cutaneous products that emphasizes quality characterization and equivalence approaches for topical medicines [16]. The European approach also recognizes that equivalence may be supported through a combination of pharmaceutical quality, in-vitro performance, permeation, pharmacodynamic, or clinical evidence depending on the product [16,25]. The continuing development of these approaches demonstrates that topical equivalence is an active regulatory-science field rather than a settled analytical problem [2,15]. For NBCDs, regulatory divergence is more visible [2,15]. Scientific literature has documented differences between the United States and European approaches to follow-on liposomes, glatiramer acetate, iron-carbohydrate complexes, and other complex products [2,7,20]. The lack of a universally harmonized definition of NBCDs can complicate comparison of regulatory requirements, because a product classified under one category in one jurisdiction may follow a different legal pathway elsewhere [20]. From a pharmaceutical-development perspective, these differences reinforce the importance of early regulatory engagement [2,15]. Applicants developing complex generics should not assume that an analytical package acceptable in one jurisdiction will automatically satisfy another authority [2,15]. Product-specific guidance, scientific advice, pre-submission meetings, and clear justification of the mechanistic relationship between CQAs and performance can reduce uncertainty [5,6]. International harmonization would be particularly valuable for Q3 characterization and in-vitro performance testing [2,15]. Differences in sampling procedures, acceptance criteria, statistical approaches, and interpretation of equivalence can increase development costs without necessarily improving scientific confidence [37,44]. Harmonization should not mean identical procedures for every product; rather, it should establish common principles for method validation, risk assessment, data interpretation, and evidence integration [2,15].

8. Quality by Design and Control Strategy for Complex Generics

Quality by Design provides a logical framework for addressing the multidimensional nature of complex drug products [13,45]. ICH Q8, Q9, and Q10 principles encourage pharmaceutical development based on product understanding, risk management, and control of critical sources of variability [45–47]. For complex generics, this approach is especially useful because formulation and process parameters may interact to determine Q3 attributes and performance [13,14]. A QbD strategy begins by defining the quality target product profile and identifying CQAs that are relevant to safety, efficacy, and performance [45]. Material attributes and process parameters are then assessed for their potential impact on these CQAs using risk assessment and experimental design [13,45]. For a topical semisolid, for example, the design space may include API particle size, excipient grade, emulsification conditions, mixing speed, temperature, and cooling profile, while CQAs may include rheology, globule size, drug state, and IVRT

behavior [31,34]. For a long-acting injectable, polymer molecular weight, particle size, drug loading, porosity, and manufacturing conditions may be linked to release kinetics and depot behavior [6,28]. The regulatory value of QbD is greatest when development knowledge is translated into a control strategy [13,45]. A control strategy should specify the material controls, process controls, in-process tests, release tests, and stability monitoring needed to maintain the relevant product attributes [13]. Q3 characterization can therefore be used not only for initial equivalence assessment but also for batch-to-batch consistency and lifecycle management [23,34]. Post-approval changes are a particularly important consideration [13,45]. If a manufacturing change modifies a Q3 attribute without changing Q1/Q2 composition, conventional composition-based comparisons may fail to detect a potential performance effect [34]. A scientifically justified Q3 and performance control strategy can provide a more sensitive basis for assessing such changes [13,45]. This is one reason why complex generics require deeper process understanding than a simple end-product testing strategy can provide [13,45].

9. Key Scientific and Regulatory Challenges

Several challenges continue to limit efficient development of complex generics [31,37]. First, many CQAs are multidimensional and difficult to measure reproducibly [31,37]. A product may differ in microstructure in ways that are detectable analytically but have uncertain clinical significance [8,23]. Second, some analytical methods lack standardized procedures or universally accepted acceptance criteria, making inter-laboratory comparison difficult [32,37]. Third, biological variability can complicate interpretation of IVPT and in-vivo studies, especially when donor skin, disease state, application technique, or local physiology contributes substantially to variability [37,38]. A further challenge is the limited availability of robust IVIVC [31,37]. Regulatory decisions are strongest when an in-vitro attribute has a demonstrated relationship with in-vivo performance, but establishing that relationship may require extensive development datasets [39,40]. For long-acting systems, the long duration of release can also make conventional development cycles slow and costly [31,37]. Another challenge is the distinction between analytical similarity and therapeutic equivalence [31,37]. A product can appear highly similar across a selected analytical panel while still behaving differently under physiological conditions, while a measurable analytical difference may have no clinically meaningful consequence [31,41]. Regulatory science therefore needs methods that are both sensitive and clinically relevant [31,37]. Finally, regulatory divergence remains an important practical issue [31,37]. Differences in terminology, application pathways, acceptance criteria, and evidence expectations can require sponsors to generate jurisdiction-specific packages [2,15,16]. Greater convergence around scientific principles, rather than rigidly identical procedures, would facilitate global development [31,37].

10. Product-Specific Regulatory Evidence Strategies

A useful way to operationalize regulatory science is to build the equivalence package around the product class rather than applying a universal testing sequence [2,13]. For topical semisolids, the central question is whether the test product reproduces the formulation structure and drug availability relevant to the local site of action [3,9]. For long-acting injectables, the key question is whether the formulation and manufacturing process produce a comparable temporal exposure profile and duration of release [6,39]. For liposomal and other NBCD products, the central issue is whether the complete structured system, rather than only the nominal drug content, is sufficiently comparable to the reference product [5,7]. This product-specific logic helps explain why regulatory evidence can legitimately differ between complex

generic categories [2,13]. For topical semisolids, Q1/Q2 information should be interpreted together with Q3 and performance data [2,13]. A generic cream may contain the same active ingredient and excipients at the same nominal concentrations but still differ in globule size, rheological behavior, drug state, or thermodynamic activity [24,31]. If these differences alter IVRT or IVPT behavior, the applicant should investigate whether they are attributable to manufacturing variability or to a meaningful formulation difference [25,34]. Conversely, a statistically detectable Q3 difference does not automatically establish therapeutic inequivalence because the clinical relevance of the difference must be considered [41]. This reinforces the importance of a predefined risk assessment connecting each attribute to product performance [2,13]. Long-acting injectables require an even stronger focus on temporal behavior [2,13]. A conventional single-time-point release measurement may fail to distinguish an early burst from a prolonged tail phase, even though both can influence clinical exposure [6]. Accordingly, release testing should cover the relevant duration and capture the phases of release that are mechanistically important [39]. The choice of release medium, agitation, temperature, sampling frequency, and sink conditions can influence the observed profile and must be justified as part of method development [40]. Where an in-vitro method is intended to support a regulatory conclusion, its discriminatory ability and relationship to in-vivo performance should be established [2,13]. For liposomes and NBCDs, orthogonal characterization is particularly important because the drug product is a structured system whose properties emerge from multiple interacting components [5,7]. Particle size alone cannot establish equivalence if lipid composition, encapsulation state, morphology, surface properties, or release behavior differ [27]. Similarly, total drug concentration does not necessarily distinguish encapsulated from free drug [2,13]. A regulatory package should therefore define a scientifically justified set of CQAs and demonstrate that the selected analytical methods can detect changes relevant to the product's mechanism [2,7]. The same principle applies to modified-release oral products and inhalation products, although their critical attributes differ [2,13]. For modified-release systems, dissolution profiles, release mechanism, dosage-form architecture, and mechanical properties may be central [18,31]. For inhalation products, aerodynamic particle-size distribution, emitted dose, device performance, and formulation-device interaction can determine lung deposition and systemic or local exposure [22]. These examples show that the concept of Q3 should be understood broadly as product-specific structural and functional characterization rather than as a fixed analytical checklist [2,13]. A practical regulatory strategy should therefore begin with four questions: what makes the product complex, which attributes control performance, which analytical methods can measure those attributes reliably, and what residual uncertainty remains after pharmaceutical and in-vitro evidence are considered [13,14]. The answers determine whether PK, PD, clinical endpoint, or additional mechanistic evidence is necessary [2,13]. This approach can reduce both under-testing and unnecessary testing by aligning the evidence package with the actual scientific uncertainty [2,13].

11. Toward a Harmonized Regulatory-Science Framework

A harmonized framework for complex generics should not attempt to impose one universal equivalence test [2,13]. Instead, it should harmonize the principles used to identify CQAs, qualify analytical methods, compare test and reference products, and determine when additional evidence is required [2,15]. The scientific foundation is already visible in current regulatory practice: agencies increasingly recognize the importance of comparative characterization and product performance, particularly for complex topical and non-biological complex products [3,16]. The remaining challenge is to translate

these principles into consistent, internationally interpretable evidence packages [2,13]. First, terminology should be aligned [2,13]. Terms such as complex generic, complex drug product, NBCD, Q3 characterization, pharmaceutical equivalence, and therapeutic equivalence are sometimes used differently across jurisdictions [2,20]. Clear terminology would reduce ambiguity when sponsors design development programs and when regulators interpret evidence [2,13]. Second, method-development principles for IVRT and IVPT should be described using common expectations for precision, specificity, discriminatory power, membrane selection, sampling, statistical analysis, and reporting [36,37]. Third, agencies should encourage transparent justification of acceptance criteria rather than relying on generic numerical thresholds that may not reflect product-specific risk [2,13]. Reference-product characterization is another important component [2,13]. If the reference product itself shows meaningful batch-to-batch variability, a single reference batch may not provide a complete picture of the acceptable product space [23]. Comparative studies should therefore consider representative reference batches where scientifically justified, particularly when the attribute under evaluation is known to vary with manufacturing history or storage [34]. This principle could help distinguish a meaningful test-product difference from normal reference-product variability [2,13]. Regulatory science should also strengthen the connection between pre-approval development and post-approval lifecycle management [2,13]. A Q3 attribute that is critical for equivalence should generally be monitored when relevant process or formulation changes are introduced [13]. This would allow analytical knowledge generated during generic development to support continued assurance of product performance [2,13]. The same principle can be applied to stability programs when product attributes are known to evolve during storage or use [5,30]. Finally, harmonization should promote early scientific dialogue [2,13]. Complex products often require product-specific interpretation, and regulators cannot reasonably provide a complete universal decision tree for every formulation technology [6]. Structured scientific advice and pre-submission engagement can allow applicants to agree on the most informative evidence package before large studies are initiated [2,13]. Over time, successful case studies can be converted into product-specific guidances and general methodological standards [2,13]. Such an adaptive regulatory-science model is more likely to keep pace with pharmaceutical innovation than a purely prescriptive system [2,13].

12. Future Perspectives

The future of complex-generic development is likely to move toward integrated evidence packages rather than single-test equivalence demonstrations [11,12]. Q3 characterization will increasingly be connected to process understanding, in-vitro performance, mechanistic modeling, and clinical pharmacology [12,14]. Advanced imaging and spectroscopic methods may provide spatial and molecular information that is currently difficult to obtain using conventional assays [11,12]. Digital and model-informed approaches may also help connect formulation variables with clinical performance, particularly when they are grounded in experimentally verified mechanisms rather than used as black-box predictors [40]. The regulatory value of such models will depend on transparency, validation, uncertainty quantification, and their demonstrated relevance to the product under assessment [11,12]. Another priority is harmonization of in-vitro methods [11,12]. Common principles for IVRT and IVPT method development, validation, statistical analysis, and reporting would improve reproducibility and make datasets more useful across jurisdictions [37,44]. Reference standards and well-characterized benchmark products could further support method qualification [11,12]. Finally, complex-generic development should be increasingly viewed as a lifecycle activity [11,12]. The evidence generated

before approval should create a scientific foundation for continued process verification, post-approval change assessment, stability monitoring, and batch consistency [13,34]. This lifecycle perspective is consistent with the broader movement toward science- and risk-based pharmaceutical regulation [11,12].

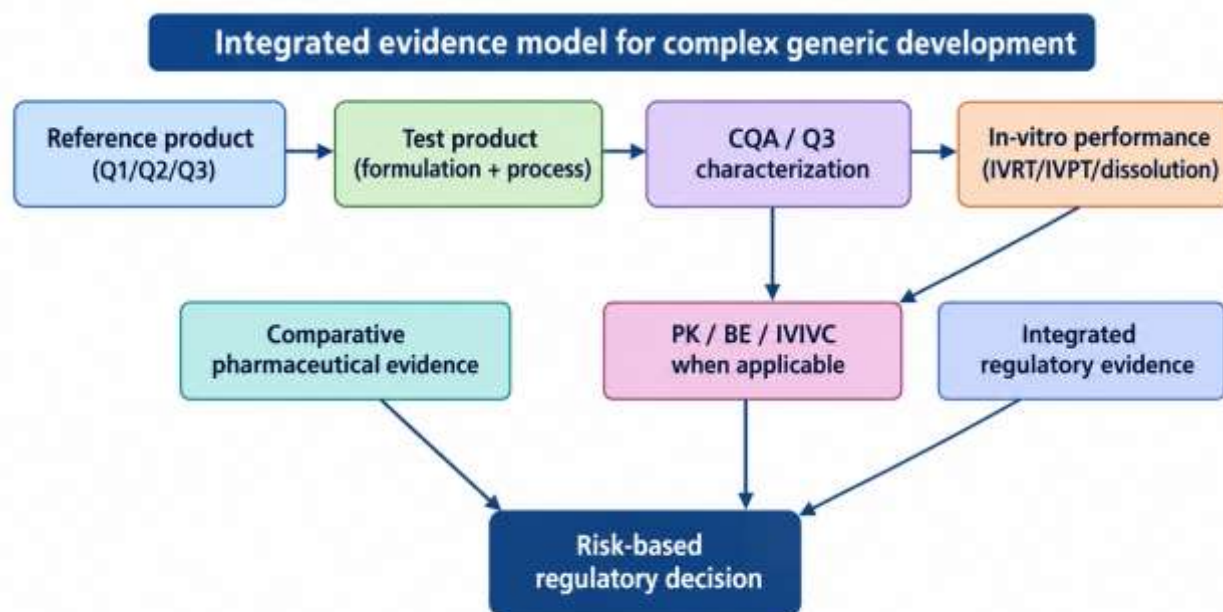


Figure 1. Integrated evidence framework linking formulation composition, Q3 attributes, in-vitro performance and bioequivalence.

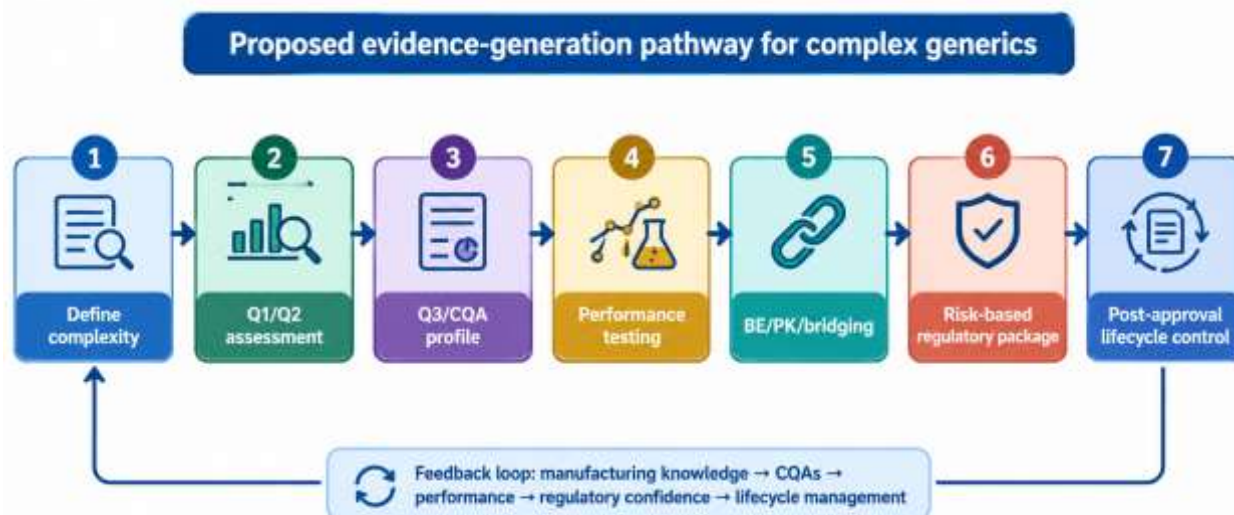


Figure 2. Proposed risk-based regulatory pathway for development and lifecycle management of complex generic products.

13. Conclusion

Complex generic drug products challenge the conventional assumption that sameness of active ingredient and dose is sufficient to predict equivalent therapeutic performance [1,2]. Their behavior may

depend on formulation architecture, microstructure, process history, release mechanisms, local disposition, or other product-specific attributes [5–8]. Q3 characterization provides an important bridge between formulation composition and functional performance, particularly for topical semisolids and other locally acting products [3,24]. However, Q3 testing should not be treated as an isolated regulatory endpoint [1,2]. Its value is greatest when the selected attributes are mechanistically linked to critical quality attributes and performance and when differences can be interpreted in the context of residual clinical uncertainty [13,31]. In-vitro release and permeation methods can provide sensitive, resource-efficient evidence, but their regulatory utility depends on validated methods, appropriate statistics, and demonstrated relevance to the route and mechanism of action [36,37]. Bioequivalence studies remain important when nonclinical evidence cannot adequately resolve uncertainty, particularly for products with complex systemic exposure or prolonged release [6,17]. A science- and risk-based framework that integrates Q1/Q2, Q3, performance, PK/BE, and lifecycle process understanding offers a practical route toward more consistent development and regulatory assessment [1,2]. Continued collaboration among pharmaceutical scientists, industry, regulators, and academia will be necessary to establish harmonized methods and evidence standards for the next generation of complex generics [1,2].

14. References

1. O'Brien MN, Jiang W, Wang Y, Loffredo DM. Challenges and opportunities in the development of complex generic long-acting injectable drug products. *J Control Release*. 2021;336:144–158. doi:10.1016/j.jconrel.2021.06.017.
2. Liu YH, Chen YS, Tseng T, Jiang ML, Gau CS, Chang LC. Regulatory considerations for generic products of non-biological complex drugs. *J Food Drug Anal*. 2023;31(1):20–31. doi:10.38212/2224-6614.3441.
3. US Food and Drug Administration. Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs: Guidance for Industry. Silver Spring, MD: FDA; 2026.
4. Miranda M, Sousa JJ, Veiga F, Cardoso C, Vitorino C. Bioequivalence of topical generic products. Part 2: Paving the way to a tailored regulatory system. *Eur J Pharm Sci*. 2018;122:264–272. doi:10.1016/j.ejps.2018.07.011.
5. Wang Y, Grainger DW. Regulatory considerations specific to liposome drug development as complex drug products. *Front Drug Deliv*. 2022;2:901281. doi:10.3389/fddev.2022.901281.
6. Panchal K, Katke S, Dash SK, Gaur A, Shinde A, Saha N, et al. An expanding horizon of complex injectable products: development and regulatory considerations. *Drug Deliv Transl Res*. 2023;13(2):433–472. doi:10.1007/s13346-022-01223-5.
7. Zagalo DM, Sousa J, Simões S. Quality by design (QbD) approach in marketing authorization procedures of Non-Biological Complex Drugs: A critical evaluation. *Eur J Pharm Biopharm*. 2022;178:1–12. doi:10.1016/j.ejpb.2022.07.014.
8. Subedar AI, Tai FM. Liposome drug development as complex pharmaceuticals: Current regulatory aspects in USA and EU. *J Generic Med*. 2026;22(1):23–40. doi:10.1177/17411343251403148.
9. Yacobi A, Shah VP, Bashaw ED, et al. Current challenges in bioequivalence, quality, and novel assessment technologies for topical products. *Pharm Res*. 2014;31(4):837–846. doi:10.1007/s11095-013-1259-1.

10. Miranda M, Cardoso C, Pais AACC, Brown M, Vitorino C. Drilling down the bioequivalence assessment of topical antifungal products: Microstructure and release. *Eur J Pharm Biopharm.* 2023;185:94–106. doi:10.1016/j.ejpb.2023.02.006.
11. Iliopoulos F, Tu D, Pence IJ, et al. Determining topical product bioequivalence with stimulated Raman scattering microscopy. *J Control Release.* 2024;367:864–876. doi:10.1016/j.jconrel.2024.02.010.
12. Iliopoulos F, Tu D, Pence IJ, et al. Raman spectroscopy as a tool to accelerate development of complex medicinal products. *J Control Release.* 2025;387:114190. doi:10.1016/j.jconrel.2025.114190.
13. Ilić T, Pantelić I, Savić S. The implications of regulatory framework for topical semisolid drug products: From critical quality and performance attributes towards establishing bioequivalence. *Pharmaceutics.* 2021;13(5):710. doi:10.3390/pharmaceutics13050710.
14. Zagalo DM, Simões S, Sousa J. Regulatory Science Approach in Pharmaceutical Development of Follow-on Versions of Non-Biological Complex Drug Products. *J Pharm Sci.* 2022;111(10):2687–2713. doi:10.1016/j.xphs.2022.07.015.
15. European Medicines Agency. Guideline on quality and equivalence of locally applied, locally acting cutaneous products. EMA/CHMP/QWP/708282/2018. Amsterdam: EMA; 2024.
16. European Medicines Agency. Guideline on the investigation of bioequivalence. CPMP/EWP/QWP/1401/98 Rev. 1/Corr. London: EMA.
17. FDA. Guidance for Industry: Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA. Silver Spring, MD: FDA; 2026.
18. FDA. Guidance for Industry: Statistical Approaches to Establishing Bioequivalence. Silver Spring, MD: FDA; 2026.
19. Schellekens H, Stegemann S, Weinstein V, de Vlieger JSB, Flühmann B, Mühlebach S, et al. How to regulate nonbiological complex drugs (NBCD) and their follow-on versions: points to consider. *AAPS J.* 2014;16:15–21. doi:10.1208/s12248-013-9533-z.
20. Crommelin DJA, de Vlieger JSB, Weinstein V, et al. Different pharmaceutical products need different regulatory approaches to establish therapeutic equivalence. *Int J Pharm.* 2015;491(1–2):e1–e4.
21. Gaspar RS, Silva-Lima B, Magro F, Alcobia A, da Costa FL, Feio J. Non-biological complex drugs (NBCDs): complex pharmaceuticals in need of individual robust clinical assessment before any therapeutic equivalence decision. *Front Med.* 2020;7:590527. doi:10.3389/fmed.2020.590527.
22. Copies of nonbiological complex drugs: generic, hybrid or biosimilar? *Drug Discov Today.* 2018;23(12):2048–2055.
23. Non-Biological Complex Drugs: Complex pharmaceuticals in need of individual robust clinical assessment before any therapeutic equivalence decision. *Eur J Pharm Sci.* 2021;156:105565.
24. Miranda M, Cova T, Augusto C, Pais AACC, Cardoso C, Vitorino C. Diving into batch-to-batch variability of topical products—a regulatory bottleneck. *Pharm Res.* 2020;37(11):218. doi:10.1007/s11095-020-02911-y.
25. Lane ME. In vitro permeation testing for the evaluation of drug delivery to the skin. *Eur J Pharm Sci.* 2024;201:106873. doi:10.1016/j.ejps.2024.106873.

26. Mohan V, Wairkar S. Current regulatory scenario and alternative surrogate methods to establish bioequivalence of topical generic products. *J Drug Deliv Sci Technol.* 2021;61:102090. doi:10.1016/j.jddst.2020.102090.
27. Miranda M, Sousa JJ, Veiga F, Cardoso C, Vitorino C. Bioequivalence of topical generic products. Part 1: Where are we now? *Eur J Pharm Sci.* 2018;123:260–267. doi:10.1016/j.ejps.2018.07.050.
28. Simões A, Miranda M, Cardoso C, Veiga F, Vitorino C. Rheology by Design: A Regulatory Tutorial for Analytical Method Validation. *Pharmaceutics.* 2020;12(9):820. doi:10.3390/pharmaceutics12090820.
29. Patere SN, Newman B, Wang Y, Choi S, Vora S, Ma AWK, et al. Influence of manufacturing process variables on the properties of ophthalmic ointments of tobramycin. *Pharm Res.* 2018;35:1–13. doi:10.1007/s11095-018-2462-x.
30. Patere S, Newman B, Wang Y, Choi S, Vora S, Ma AWK, et al. Influence of manufacturing process variables on the properties of ophthalmic ointments of tobramycin. *Pharm Res.* 2018;35.
31. Quality and equivalence of topical products: A critical appraisal. *Eur J Pharm Sci.* 2020;148:105082. doi:10.1016/j.ejps.2019.105082.
32. Chang RK, Raw A, Lionberger R, Yu L. Generic development of topical dermatologic products: Formulation considerations. *AAPS J.* 2013;15:41–52.
33. Shah VP, Yacobi A, Rădulescu FS, Miron DS, Lane ME. A science based approach to topical product bioequivalence. *Pharm Res.* 2015;32:2037–2044.
34. Namjoshi S, Dabbaghi M, Roberts MS, Grice JE, Mohammed Y. Quality by design: Development of the topical semisolid dosage form. *Pharmaceutics.* 2020;12:287.
35. Supe S, Takudage P. Methods for evaluating penetration of drug into human skin: A review. *Skin Res Technol.* 2021;27:299–308.
36. Rath S, Kanfer I. A validated in vitro release test for topical semisolid formulations. *Pharm Dev Technol.* 2020;25:1–10.
37. Khatana S, Dhaneshwar SS, Sharma A. In vitro release testing of topical semisolid dosage forms: Methodological considerations. *J Pharm Innov.* 2022;17:1–15.
38. Franz TJ. Percutaneous absorption. On the relevance of in vitro data. *J Invest Dermatol.* 1975;64:190–195.
39. OECD. Guidance document for the conduct of skin absorption studies. OECD Series on Testing and Assessment. Paris: OECD; 2004.
40. Bao Q, Newman B, Wang Y, et al. In vitro release testing method development for long-acting injectable suspensions. *Int J Pharm.* 2022;624:121990.
41. Bao Q, et al. Development of in vitro-in vivo correlations for long-acting injectable suspensions. *Int J Pharm.* 2023;635:122719.
42. Malavia N, Burgess DJ. Insights into development of long-acting injectable suspensions. *Int J Pharm.* 2026.
43. Challenges and complications of poly(lactic-co-glycolic acid)-based long-acting drug product development. *Pharmaceutics.* 2022;14:2042.
44. Long-acting injectable formulation technologies: Challenges and opportunities for the delivery of fragile molecules. *Expert Opin Drug Deliv.* 2022;19:1–17.
45. Complement activation as a bioequivalence issue relevant to the development of generic liposomes and other nanoparticulate drugs. *Biochem Biophys Res Commun.* 2015;468:504–510.

46. Vigani A, et al. Regulatory considerations for liposomal drug products and nanomedicines. *Int J Pharm.* 2020;586:119551.
47. Colombo P, Bettini R, Santi P, De Ascentiis A, Peppas NA. Analysis of the swelling and release mechanisms of hydrophilic matrices. *J Control Release.* 2000;65:1–13.
48. ICH. Pharmaceutical Development Q8(R2). International Council for Harmonisation; 2009.
49. ICH. Quality Risk Management Q9(R1). International Council for Harmonisation; 2023.
50. ICH. Pharmaceutical Quality System Q10. International Council for Harmonisation; 2008.