veeda clinical research®

Charting A New Way- Complex Generics and 505(B)(2) Regulatory Pathways

How are Complex Generics Different from Simple Generics?

U.S. Food and Drug Administration (FDA) definition

Simple generic is identical – or bioequivalent – to a brand name drug in dosage form, safety, strength, route of administration, quality,performance characteristics and intended use

A complex generic could have a complex active ingredient, complex formulation, complex route of delivery, or complex drug device combinations

European Medicines Agency (EMA) definition

A generic drug is a medicine that is developed to be the same as a medicine that has already been authorized. It contains the same active substances and is used at the same doses to treat the same diseases as the reference drug

EMA refers to complex generics as “hybrid medicines,” whose “authorization depends partly on the results of tests on the reference medicine and partly on new data from clinical trials."

Examples of Complex Generics

Complex active ingredients	E.g., Complex mixtures of APIs, polymeric compounds, peptides, naturally sourced ingredients
Complex formulations	E.g., Liposomes, suspensions, emulsions, gels, parenteral microspheres, colloids
Complex routes of delivery	E.g., Locally acting such as ophthalmic, otic, dermatological, locally acting GI drugs and inhalational drugs
Complex dosage forms	E.g., Long-acting injectables and implants
Complex drug-device combinations	E.g., Metered Dose Inhalers, nasal sprays, dry powder inhalers and transdermals

Other products where complexity or uncertainty concerning the approval pathway or other alternative the approach would benefit from early scientific engagement

FDA Regulatory Framework for Complex Generics

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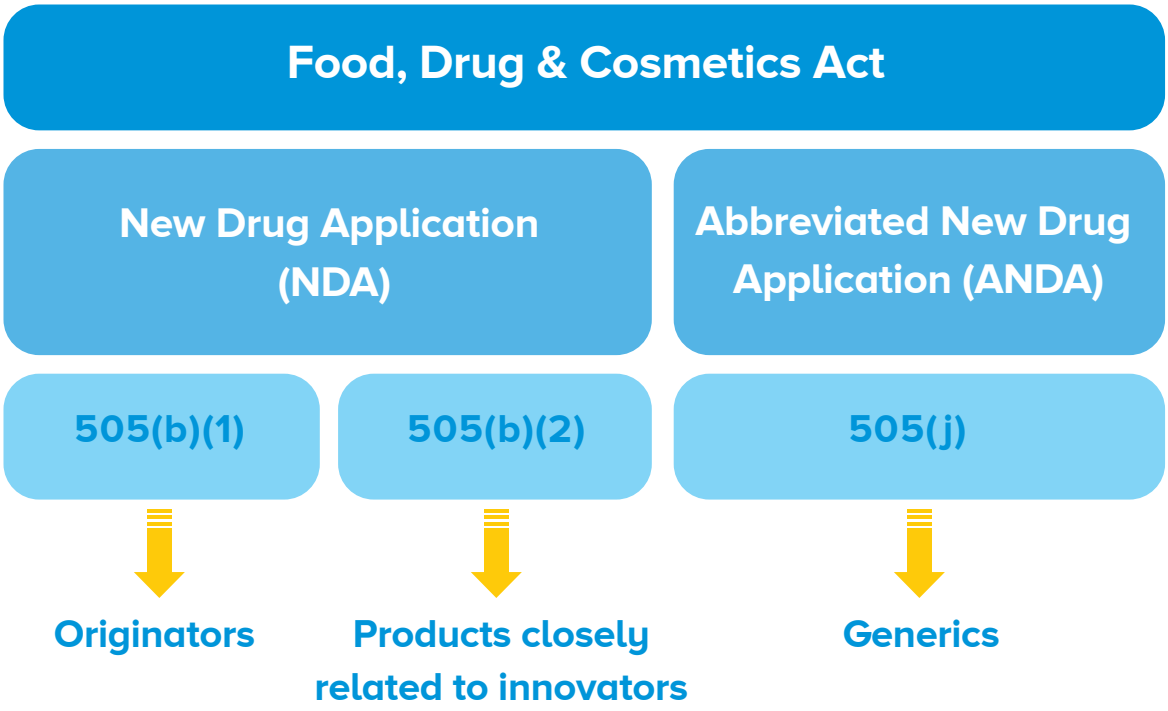

The Office of New Drugs (OND) is responsible for all 505(b)(2) applications as opposed to the Office of Generic Drugs (OGD) for 505(j) applications

505(b)(2) application may provide greater flexibility in study types, supporting data and information or may require additional clinical studies to establish further efficacy and safety profiles

Types of Applications Allowed Under 505(b)(2)

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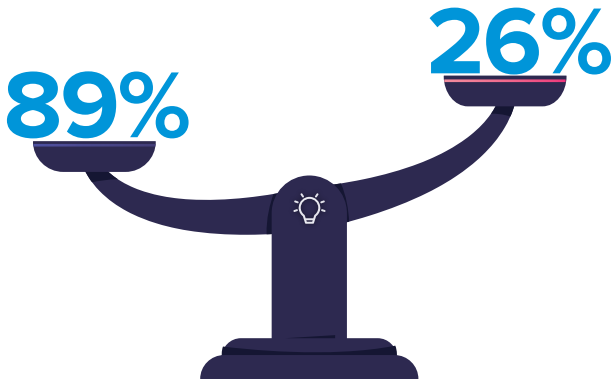
MODIFICATIONS	EXAMPLES
Route Of Administration	Intravenous to oral administration
Change In Active Ingredient	Different salt, racemate, enantiomer
Dosage Form	Oral to transdermal patch
Strength	Lower or higher strength
Combinations	Change one ingredient in a previously approved combination or a new combination of previously approved drugs
Formulation	Lower or higher strength
Dosing Regimen	Change from twice daily to once daily
New Molecular Entity	Prodrug of a previously approved drug
Indication	Expansion of diseases drug is approved for OTC A previously approved drug switched to OTC or change in an existing OTC drug
Naturally Derived Or Recombinant Product	A new form of the approved drug from a new manufacturing source (not biologics)
Bioinequivalence	Controlled-release version of a drug

Market Opportunities

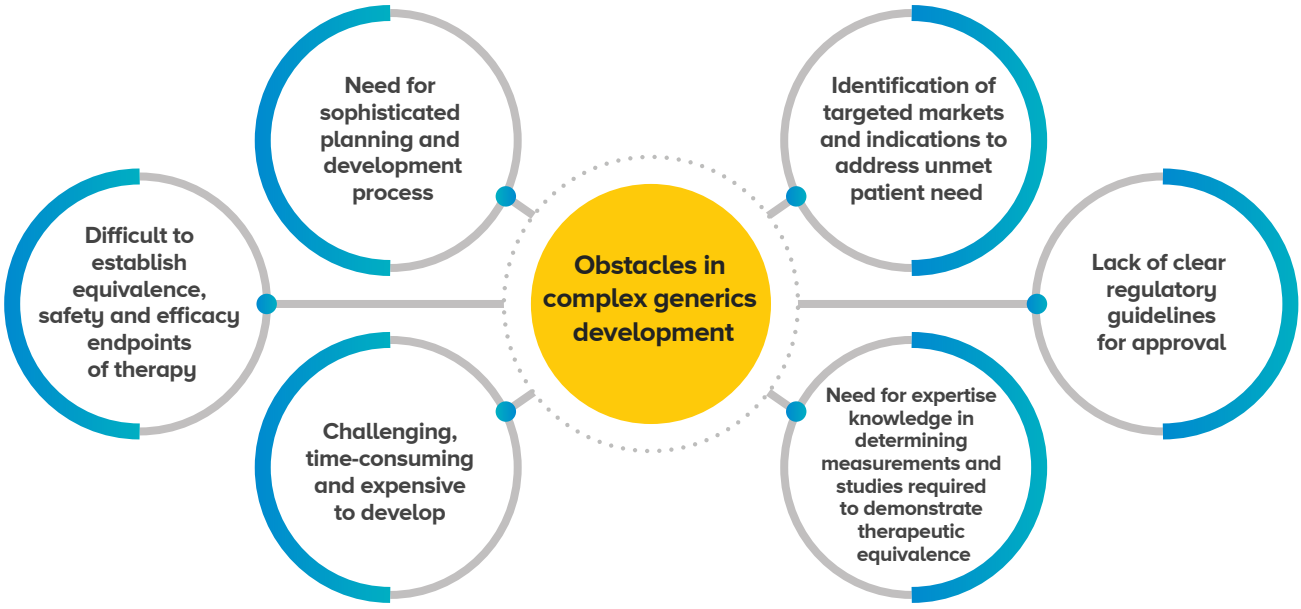
Generic drugs are in high demand globally due to their affordability to the common masses as compared to branded drugs. In the US healthcare market, generics account for 89% of all prescriptions but account for just 26% of the cost as compared to branded drugs.



As the market has become saturated with simple generics and the number of drugs coming off patent continues to decline drastically, pharma companies are now building their capabilities in developing complex generics.

Complex generics aim to solve existing or additional unmet needs of the patient. Complex generics are a good opportunity for pharma companies to earn higher revenues and achieve market differentiation.

Key Challenges in Developing Complex Generics



Reality Check: 505(b)(2) Approvals Over the Recent Past

The number of approvals has been consistent over the recent past. A publication by Freije I, et al, 2019 revealed the following facts

1. A total of 226 drugs were approved between 2012 and 2016 under 505(b)(2) application

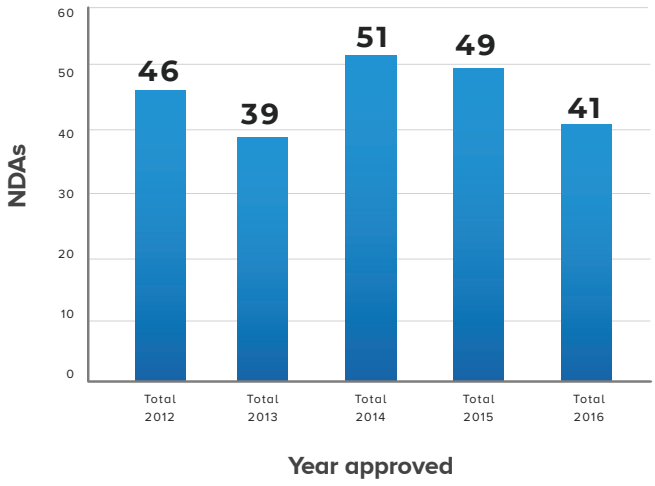


Figure 1. Number of 505(b)(2) approvals per year from 2012 to 2016.

2. Most drugs approved included a new formulation or new manufacturer, followed by a new dosage form and a new combination.

Type 1-New molecular entity (NME), Type 2 - New active ingredient, Type 3-New dosage form, Type 4-New combination, Type 5-New formulation or new manufacturer, Type 6-New indication, Type 7-Drug already marketed without an approved NDA, Type 8-Over-the-counter (OTC) switch, Type 10 -New indication submitted as distinct NDA- not consolidated

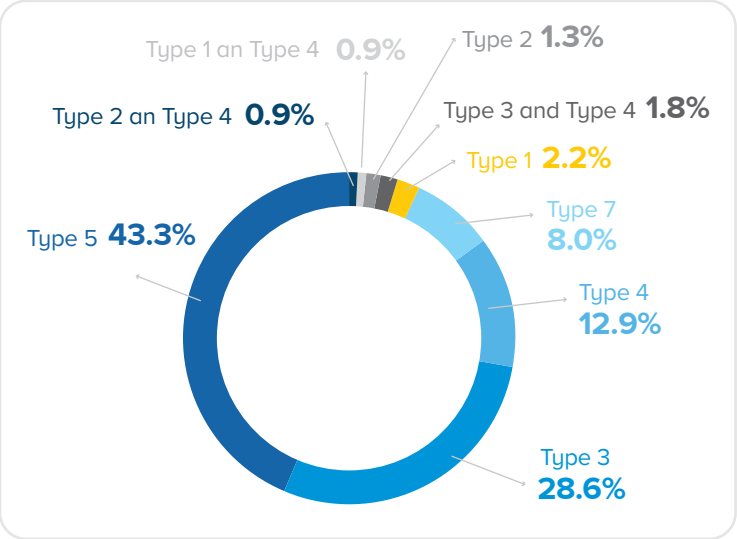


Figure 2. FDA submission classification of drug products approved via 505(b)(2) pathway from 2021 to 2016 (n=224). Refer to Table 1 for FDA submission classification types.

Table 3. Bridging Approaches

Bridging Approaches	NDAs (%)
Preclinical	5 (3.9)
Single-dose BA/BE	78 (69.6)
In vivo BA/BE waiver	25 (20)
PK/PD	3 (2.3)
Dose proportionality	1 (0.7)
Total	**112**

3. For most of these applications, a scientific bridge was established by a single-dose BA/BE study comparing the PK of the new product and RLD

Source: Freije I, Therapeutic Innovation & Regulatory Science, 2019.

Abbreviations: BA/BE, bioavailability, bioequivalence; NDAs, new drug applications; PK/PD, pharmacokinetics/ pharmacodynamics

Key Considerations

Candidate Identification and assessment

- Nonclinical studies-favourable PK profile
- Assessing scientific, medical, regulatory and commercial viability

Regulatory requirements

- Product specific guidance (PSG) from the FDA Office of Generic Drugs (OGD), European Medicines Agency's (EMA)
- Interactions with regulatory agencies and precedents: trial parameters, data end points

Study design and planning

- Protocol, study design, location(s), population Right collaboration for clinical studies
- Approval from local regulatory bodies

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How can Veeda Support you in Complex Generics Development?

- Veeda Clinical Research Limited (“Veeda”) together with its subsidiary, Bioneeds India Private Limited (“Bioneeds”), and its joint venture, Ingenuity BioSciences Private Limited (“Ingenuity”), (together referred to as the “Veeda Group”) offers a comprehensive portfolio of clinical, preclinical and bio/analytical services to support innovator, biosimilar and generic drug development programs of our global clientele

- We are an independent, institutional investors owned, board governed and professionally managed contract research group offering scientific leadership, global quality management systems and long term operational and financial stability through a continuing investment in our people, processes, systems, infrastructure and technology and a deep commitment to quality

- Together, we serve clients globally in the following industries:
  - Pharmaceutical and Biopharmaceutical
  - Agrochemical and Industrial Chemicals
  - Herbal/Nutraceuticals
  - Medical Devices

Veeda can Support you in

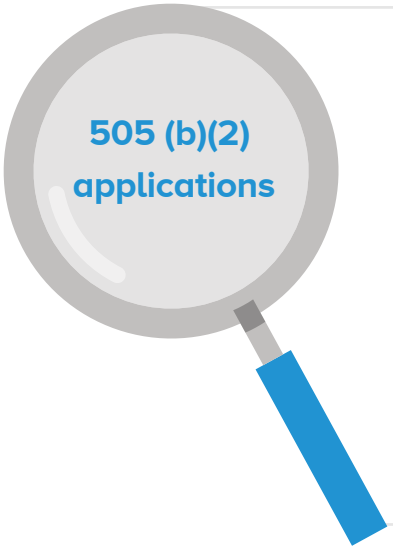
Study design and planning

- Clinical study design, development of study protocol
- Approval from local regulatory bodies and Ethics committee

Compliance

- Cost effective quality execution in timely manner

Our Capabilities in Supporting 505(b)(2) Applications



Clinical Studies

- Single & multiple dose BA/BE
- Dose proportionality
- Pharmacokinetics/Pharmacodynamics
- Food effect
- Safety/ efficacy studies
- Drug drug interaction
- Single ascending dose/ multiple ascending dose

Pre-Clinical Studies

- Pre clinical

In Vitro Studies

- In vivo – Bio waiver
- In vitro dose dumping studies
- In vitro PD studies

505(b)(2) Veeda Experience

Veeda CR has been a partner in supporting 505(b)(2) applications with ~45 studies experience with various clients.

505 (b)(2)	Test	RLD	Design
Salt change	Drug hermitartrate tablets	Drug mesylate tablets	Single Dose BE
Change in formulation and dosage form	Drug 300 mg ER tablets	Drug 150 mg IR capsules (2x150 mg)	Comparative BA
Change in formulation and strength	Drub sublingual tablets 0.6 mg	Drug tablets 1 mg	Comparative BA
Change in formulation	Drug ODT 2 mg	Drug tablets 2 mg	Single Dose BE

505 (b)(2)	Test	RLD	Design
FDC	Fixed dose combination of statin and cholesterol-lowering agent	Individual formulations of statin + cholesterol -lowering agent	Single dose BE
FDC	Fixed dose combination of statin and cholesterol-lowering agent	Individual formulations of statin + cholesterol -lowering agent	Single dose BE
Change in formulation	Statin drug oral suspension 20 mg/5 ml (total dose – 80 mg)	Drug tablets	Single dose BE
Change in formulation	Drug 20 mg soluble tablets	Drug tablets 2.0 mg (2.0 mg x 10)	Comparative PK study
Strength change	Drug 600 mg PR tab	Drug XR tablets 200 mg (3 tablets x 200 mg)	Multiple dose BE

Bioanalytical Research Capabilities and Experience

We have 77 bioanalytical methods available for complex generics

Types of methods

- Capability to develop methods with lowest quantification level – up to 0.1 pg
- Methods developed for:
  - Endogenous molecules
  - Amino acids (Multiple analysis in single injection)
  - Hormones
  - Steroids
  - Inhalation formulation
  - Elemental bioanalysis (Other matrix – Urine)
  - Immunogenicity
  - Large molecules/ ECLIA/ ELISA
  - Chiral and Liposomal
- Tissue distribution studies

We have state-of-the-art Clinical Infrastructure facilities

Scale and Range

46 LC-MS/MS machines

- Insignia (33) and Vedant (13)
- API 5500/4000/3200/3000/2000
- Shimadzu 8060/8050/8040
- Quattro Premier

2 ICP-OES

Watson LIMS

Storage Capacity

Plasma Sample:

- 45 deep freezers with capacity to store 11,25,000 samples at -80°C

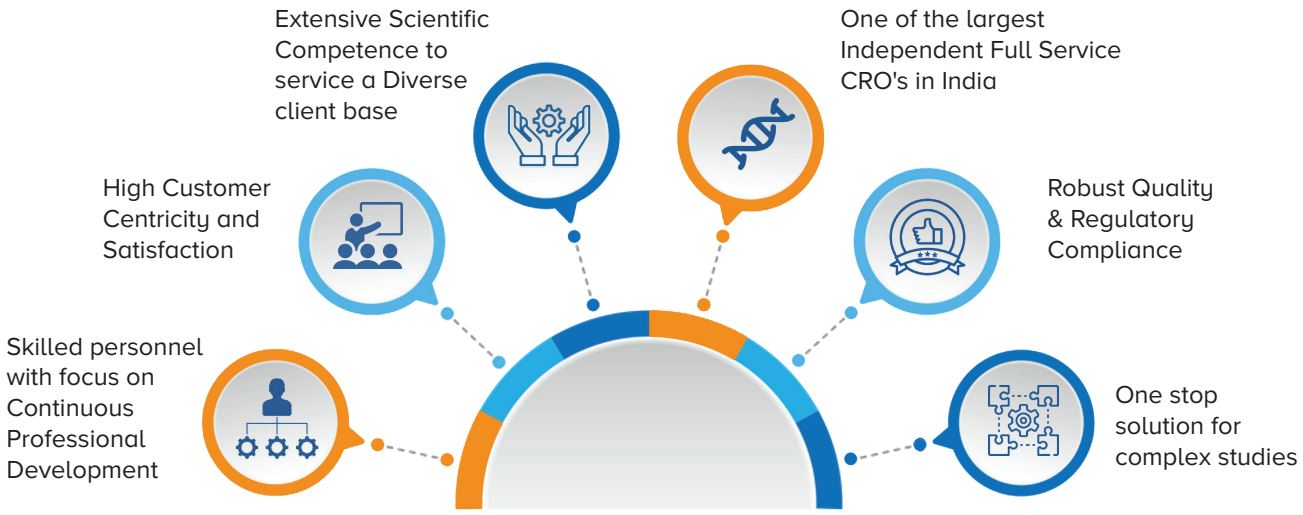
IP Storage

- 3 walking type stability chambers with overall capacity to store 34000 ltr for retention at room temperature
- 4 humidity chambers with overall capacity of 3200 ltr
- 4 pharmaceutical refrigerators having storage capacity of 3550 ltr at 2-8°C

Complex Methods Experience

- **Iron Sucrose:** For Transferrin bound iron the serum samples are filtered through SPE cartridges to remove free and formulation bound iron while the filtrate contains TBI which is further analyzed by ICP OES.
- **Peptides (small molecules) by LCMSMS:** sensitivity and extraction issues
  Desmopressin
  Leuprolide
  Octreotide
- **Biomarker analysis - α1 Acid Glycoprotein – AAG:** Method HPLC-UV, large molecule (biomarker) validated method for clinical support
- **Liposomal formulations** i.e Doxorubicin, Amphotericin
- **Inhalalation products:** Formoterol

Veeda Group Advantage



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To know more about our Complex Generics capabilities, mail us at **info@veedacr.com**

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