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**

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

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

505(j) requirements:
- Toxicology and clinical data not required
- Exclusivity: 180 days
- Timings: 1-2 years
- Cost: $50k-$750k

505(b)(2) requirements:
- Toxicology and clinical data may or may not be required
- Exclusivity: 3 or 5 years
- Timings: 2-5 years
- Cost: $3m-$7m
Types of Applications Allowed Under 505(b)(2)

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.

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**

- **Obstacles in complex generics development**
  - Need for sophisticated planning and development process
  - Identification of targeted markets and indications to address unmet patient need
  - Challenging, time-consuming and expensive to develop
  - Lack of clear regulatory guidelines for approval
  - Difficult to establish equivalence, safety and efficacy endpoints of therapy
  - Need for expertise knowledge in determining measurements and studies required to demonstrate therapeutic equivalence

**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.](image)
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

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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


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

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**Table 3. Bridging Approaches**

<table>
<thead>
<tr>
<th>Bridging Approaches</th>
<th>NDAs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>5 (3.9)</td>
</tr>
<tr>
<td>Single-dose BA/BE</td>
<td>78 (69.6)</td>
</tr>
<tr>
<td>In vivo BA/BE waiver</td>
<td>25 (20)</td>
</tr>
<tr>
<td>PK/PD</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>Dose proportionality</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Total</td>
<td>112</td>
</tr>
</tbody>
</table>

**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.

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**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

**Candidate Identification and assessment**

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

**Study design and planning**

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

### How can Veeda Support you in Complex Generics Development?

- 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

505(b)(2) Veeda Experience

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

<table>
<thead>
<tr>
<th>505 (b)(2)</th>
<th>Test</th>
<th>RLD</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salt change</td>
<td>Drug hermitartrate tablets</td>
<td>Drug mesylate tablets</td>
<td>Single Dose BE</td>
</tr>
<tr>
<td>Change in formulation and dosage form</td>
<td>Drug 300 mg ER tablets</td>
<td>Drug 150 mg IR capsules (2x150 mg)</td>
<td>Comparative BA</td>
</tr>
<tr>
<td>Change in formulation and strength</td>
<td>Drub sublingual tablets 0.6 mg</td>
<td>Drug tablets 1 mg</td>
<td>Comparative BA</td>
</tr>
<tr>
<td>Change in formulation</td>
<td>Drug ODT 2 mg</td>
<td>Drug tablets 2 mg</td>
<td>Single Dose BE</td>
</tr>
</tbody>
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<tr>
<td>FDC</td>
<td>Fixed dose combination of statin and cholesterol-lowering agent</td>
<td>Individual formulations of statin + cholesterol-lowering agent</td>
<td>Single dose BE</td>
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<td>Single dose BE</td>
</tr>
<tr>
<td>Change in formulation</td>
<td>Statin drug oral suspension 20 mg/5 ml (total dose – 80 mg)</td>
<td>Drug tablets</td>
<td>Single dose BE</td>
</tr>
<tr>
<td>Change in formulation</td>
<td>Drug 20 mg soluble tablets</td>
<td>Drug tablets 2.0 mg (2.0 mg x 10)</td>
<td>Comparative PK study</td>
</tr>
<tr>
<td>Strength change</td>
<td>Drug 600 mg PR tab</td>
<td>Drug XR tablets 200 mg (3 tablets x 200 mg)</td>
<td>Multiple dose BE</td>
</tr>
</tbody>
</table>
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/ ECLI/ 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
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

Inhalation products: Formoterol

References
5. https://www.nuventra.com/resources/blog/what-is-505b2/

Veeda Group Advantage

- Skilled personnel with focus on Continuous Professional Development
- High Customer Centricity and Satisfaction
- Extensive Scientific Competence to service a Diverse client base
- One stop solution for complex studies
- Robust Quality & Regulatory Compliance
- One of the largest Independent Full Service CRO’s in India

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

Partners in creating a Healthier Tomorrow