PLENARY 2

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"IP issues for consideration in development of generic formulations for LMICs"

"Protecting IP is a vital part of fostering continued innovation ... This innovation must be accessible to people globally"

Role of intellectual property (IP)

Opportunity. IP drives economic growth, promotes innovation, and safeguards the hard work of inventors.

- Turns ideas into profit-making assets.
- Protects exclusive rights over novel products or brands.
- Forms an essential part of the branding strategy.
- Enhances the market value of products.
- Gives the business an edge over competitors.
- Raises money by out-licensing or selling IP.
- Encourages innovation and rewards innovators or entrepreneurs.
- Enhances chances of joint ventures and collaboration.

Challenge. IP often delays the introduction of generic products.

- Determines the earliest possible launch date.
- Helps identify the product's patent and technology landscape.
- Patent clearance is mandatory before finalizing a generic development plan to avoid or minimize future legal uncertainty.
- IP strategy should be in place before generic dossier filing to minimize risk of delayed generic launch.

IP layers relevant to generic development

Data Exclusivity (DE).

- First barrier to generic development.
  - ◊ Prevents generic manufacturers from relying on the original filer's preclinical and clinical trial data for a specific period.
  - ◊ Examples: New chemical entity exclusion (US); Data and Market exclusivity (EU); Re-examination period (Japan).
  - ◊ Typically, DE ranges from 5 to 10y (Up to 15y for an orphan drug) starting from market approval date and ending as per local law.
    - * Berdazimer sodium: New Chemical Entity exclusivity expires Jan 5, 2029 in US.
    - * Momelotinib: Orphan drug exclusivity expires Jan 26, 2034 in EU.
- Important considerations.
  - ◊ **Not classified under IP but offers the strongest form of protection for brands**.
  - ◊ **In the absence of a patent, DE can be a constraint for generic launch.** Generic approval is not possible without brand drug approval.
  - ◊ Key topic in discussions related to trade agreements (NAFTA, EU-India Free Trade Agreement).
  - ◊ Data on DE are provided by some countries. For the remaining countries, it is calculated based on market approval date.

Patents.

- Most widely used IP tool to increase value and prevent competitors. (I.e., Protect and leverage innovations)
  - ◊ Examples: API patent; Process patent; Composition patent.
- Important considerations.
  - ◊ Play a key role in product life cycle management. Enable brands to maintain market exclusivity.
  - ◊ Brands often seek to extend patent monopolies as long as possible. Maximize profitability.
  - ◊ Patents are territorial. Generics must consider patent status in manufacturing and export countries.
  - ◊ Patents may come from the innovators or third parties.
  - ◊ Generic developers must consider all patents for a given product. Expiration timelines vary.
- Most relevant patent types for generic formulations.

API	Technology	Composition	Indication	Process	Polymorph	Dosage Regimen
Combination	Drug Delivery System	Salt/Ester	Particle Size	Analytical Method	Packaging	Device

* **Red** indicates the most significant risk for delayed generic entry.

  - ◊ **API patents are the strongest barrier.** No generic product is possible until API patent expiration.
  - ◊ **Formulation patents are a significant barrier for complex generic LAI products.**

Registered design.

- Examples: Device, Autoinjector, and Pen designs.

Trade secrets.

- Exact manufacturing process or method of analysis. Even when processes are disclosed, details are often unclear. It is difficult for generic developers to replicate the desired specifications.

Generic LAI case studies

	VIVITROL (Naltrexone LAI)	RISPERDOL CONSTA (Risperidone LAI)	INVEGA SUSTENNA (Paliperidone palmitate LAI)
Approval and patent landscape[1]	• API patent expired before brand approval (2006). • 20 patents with expirations from 2017-2019.	• API patent expired 3y after brand approval (2003). • 19 patents with expirations from 2008-2020.	• API patent expired 5y after brand approval (2009). • All other patents expired by 2019, except one set to expire in 2031.
Rate limiter	**Composition-dose patent.** • Last patent to expire in 2019. • Independent claim 1 is related to the dosage (Naltrexone 130-480mg) and polymer used to prepare the formulation.	**Patent thickening and technology.**	**Dosage and administration patent.** • Last patent to expire in 2031. • Independent Claim 2 is related to the specific dosing regimen in adults.[2] • Drug product hydrolyzes to API; US product label (2024) recommends product dosing that corresponds to dosages already claimed.
First generic launch	**20y after brand approval even without an API patent.** • ANDA submitted by Teva in July 2020 . • Teva and Alkermes settled on a generic launch date in Jan 2027.	**20y after brand approval and 2-3y after all patents expired.** • No ANDA filed with paragraph IV certification.[3] • First generic product approved in 2023.	**Delayed until 2031 pending court decision on patent validity.** • ANDA submitted in 2018 and was approved in 2020 • **Teva contested the validity of the last remaining patent.[4]** • 505(b)(2) product was recently approved (ERZOFRI by Luye).
Takeaways	• A specific composition patent with dose can give innovators an advantage to maintain a monopoly and significantly delay generic launch.	• Generics were unable to develop a non-infringing composition. • Technical challenges exist, including BE, even with the same composition as the brand product.	• Dosage and administration patents are among the strongest IP tools for innovators to delay generic launch. • There is no possibility to change the dose/dosage of the generic label.

[1] Patent information from the FDA Orange Book.

[2] Two loading doses (150 mg-eq IM on day 1 and 100 mg-eq IM on day 8) and monthly maintenance dose (25 to 150 mg-eq IM), which correspond to the US product label (234mg IM on day1 and 156mg IM on day 8 and monthly maintenance of 39-234mg or 78-234mg IM).

[3] No patent challenge or assertion of non-infringing composition.

[4] District Court of New Jersey upheld the patent validity in 2021; US Court of Appeals for the Federal Circuit rendered a split decision in 2024; Affirmed the indefiniteness determination but vacated the non-obviousness determination. Teva has one more opportunity to prove patent invalidity.

Insights for generic development

IP poses significant hurdles for achieving non-infringing formulations.

- Technology-related patents, especially if core drug technologies are protected.
- Coverage of excipients with unique properties (e.g., PGLA). Alternative products may fail to mimic the desired effected, leading to BE issues.
- Claiming all possible stability options.
- Claiming a specific particle size or drug-polymer ratio. Deviations from the RLD can lead to altered dissolution profiles with potential for BA failures or patient compliance issues.
- Protecting particle size, viscosity, and PH make it difficult to meet regulatory requirements for these characteristics without infringing.
- Trade secrets in the manufacturing process. Even when patents disclose a process, the exact details are often unclear, making it hard to replicate the desired specifications.
- Reproducibility of complex products, such as LAIs.

Options for generic developers.

- Begin development as early as possible and consider filing novel IP if there is patentability in the non-infringing product.
- Try an alternative technology with no IP or with IP that will expire before the API patent.
- Collaborate with innovators and developers in the same field and global stakeholders.
- Check patent status in the target commercial territory and manufacturing country.
- Check patent validity and explore whether the IP can be successfully circumvented or contested (More relevant for a secondary patent or incremental invention).
- Consider obtaining a license for the IP in countries where the innovator has limited commercial interest (Best option without any legal uncertainty).
- Explore voluntary, public health licensing.