Patent Implications for Generic Drug Development

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What is Intellectual Property?

What is Intellectual Property?

Simply……..Creations of the mind

“Creative works or ideas embodied in a form that can be shared or can enable others to recreate, emulate, or manufacture them.’

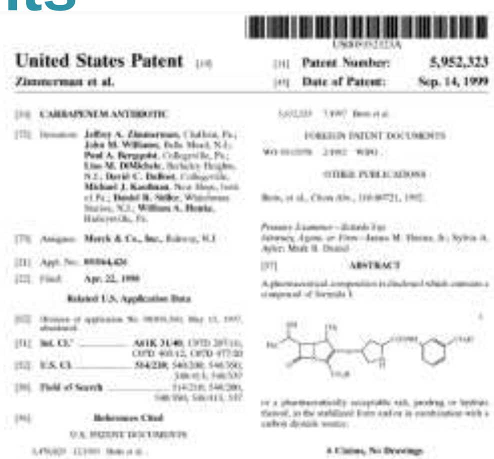
US Patent and Trademark Office

What is Intellectual Property?

Examples of intellectual property include:

- **Trademarks**

- **Patents**



United States Patent
Zimmerman et al.
Patent Number: 5,952,323
Date of Patent: Sep. 14, 1999

- **Copyrights**
  - Music, movies, slogans, etc
- **Trade secrets**
  - Non-public information held within the company
- **Contracts**
  - Supply agreements, etc

What is a Patent?

Patent – contract with a state

- **State grants to the inventor the exclusive right to prevent others from making, using, or selling the invention for a limited period.**

- **Inventor must make a full disclosure of the invention.**

- **After the patent's expiration, the Inventor loses its exclusive right to manufacture the drug and prevent others from making and selling the invention.**

Global nature of patents

- **New innovative medicines are typically protected by patents.**
  - 20 yr term from the filing (or priority date) of the patent application
- **Most countries have established mechanisms to provide protection to individuals / companies that establish valid patents.**
- **Patent protection is only able to be enforced within the jurisdiction of that country.**
  - For example, a patent granted in the US is only valid in the US and not the EU.

Implication → Generic companies need to evaluate innovator and 3rd party patents in each country that they seek to market in.

US Hatch-Waxman Act

- Hatch-Waxman Act was passed in 1984 in the US.
- Formed the basis for the current generic drug industry in the US.
- Provided benefits for brand and generic manufacturers[2]:

Generic Manufacturers

- Created ANDA approval pathway – Generic can leverage brand's safety and efficacy data for approval (must demonstrate bioequivalence).
- Allows testing of the brand product before patent expiry.
- Created 180-day exclusivity for 1st successful generic para IV challenge

Brand Manufacturer

- 30 month stay on generic company's ANDA with para IV litigation on Orange Book listed patent.
- Defined conditions for patent term extensions.
- Created multiple pathways to obtain exclusivity.

Innovative products can be eligible for various exclusivities granted by health authorities

- **Exclusivity is granted by government agencies (FDA in the US) upon approval of a drug**
  - Exclusivity was designed to promote a balance between new drug innovation and generic drug competition

Exclusivities available from Hatch-Waxman Act		
New Chemical (NCE)	5 years	At NDA approval
Orphan Drug (ODE)	7 years	At NDA approval
Pediatric Exclusivity	6 months	Added to existing patent life or exclusivity
Change (such as new formulation)	3 years	At the time of the change approval

How do patents impact generic drug development in the US?

- **US Food and Drug Administration (FDA) requires patent information to be submitted with new drug applications (NDA).**
  - In most other countries, patent status is not tied to the ability for a generic product to obtain health authority approval.

- **US FDA will publish the submitted patent information in the Orange Book upon NDA approval.**

- **Generic applicants that file ANDAs will need to 'certify' to each of the Orange Book listed patents for the Reference Listed Drug.**

US FDA Orange Book

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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Additional Information about Patents

- Patent information is published on or after the submission date as defined in 21 CFR 314.53(d)(5).
- Patent listings published prior to August 18, 2003, only identify method-of-use claims. The listed patents may include drug substance and/or drug product claims that are not indicated in the listing.
- As of December 5, 2016, an NDA holder submitting information on a patent that claims both the drug substance and the drug product (and is eligible for listing on either basis) is required only to specify that it claims either the drug substance or the drug product. Orange Book users should not rely on an Orange Book patent listing, regardless of when first published, to determine the range of patent claims that may be asserted by an NDA holder or patent owner.

Patent and Exclusivity for: N021337

Product 001
ERTAPENEM SODIUM (INVANZ) INJECTABLE EQ 1GM BASE/VIAL

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
001	5952323*PED	11/15/2017					

Exclusivity Data

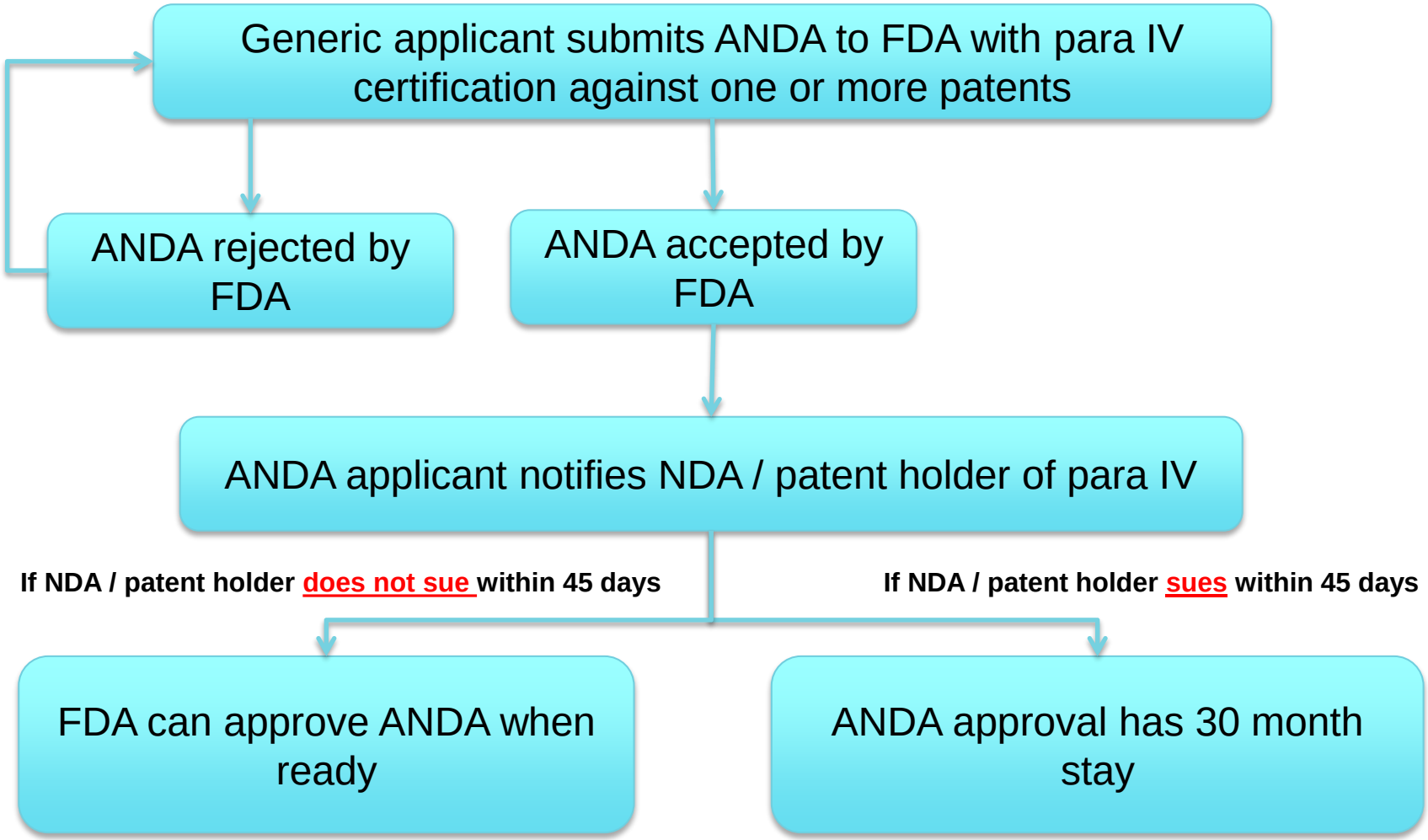
Product No	Exclusivity Code	Exclusivity Expiration

There is no unexpired exclusivity for this product in the Orange Book database.

Types of patent certifications in the US[5]

- **Paragraph I**
  - Patent information has not been filed with the FDA.
  - FDA can approve ANDA when ready
- **Paragraph II**
  - The patent has expired.
  - FDA can approve ANDA when ready
- **Paragraph III**
  - The date the patent will expire
  - FDA can approve ANDA when patent expires and ANDA is ready
- **Paragraph IV**
  - The patent is invalid or not infringed by the drug product proposed in the ANDA
  - Complex approval landscape

What happens after a generic company files paragraph IV certification?



What happens after a generic company files paragraph IV certification?

- **ANDA approval depends on patent litigation:**

Litigation Status	Regulatory Action
Lawsuit pending before 30-month stay expires	FDA can only tentatively approve ANDA
Lawsuit still pending at 30 months	FDA can approve ANDA
Dismissal / Settlement	FDA can usually approve ANDA on agreed date
Brand wins	FDA can only tentatively approve ANDA until patent expires

Benefits of being first-to-file paragraph IV

- **Incentive created within Hatch-Waxman Act to challenge patents and bring forward generic market entry.**

- **If an ANDA applicant is the first to file paragraph IV, they can be eligible for 180-day exclusivity.**

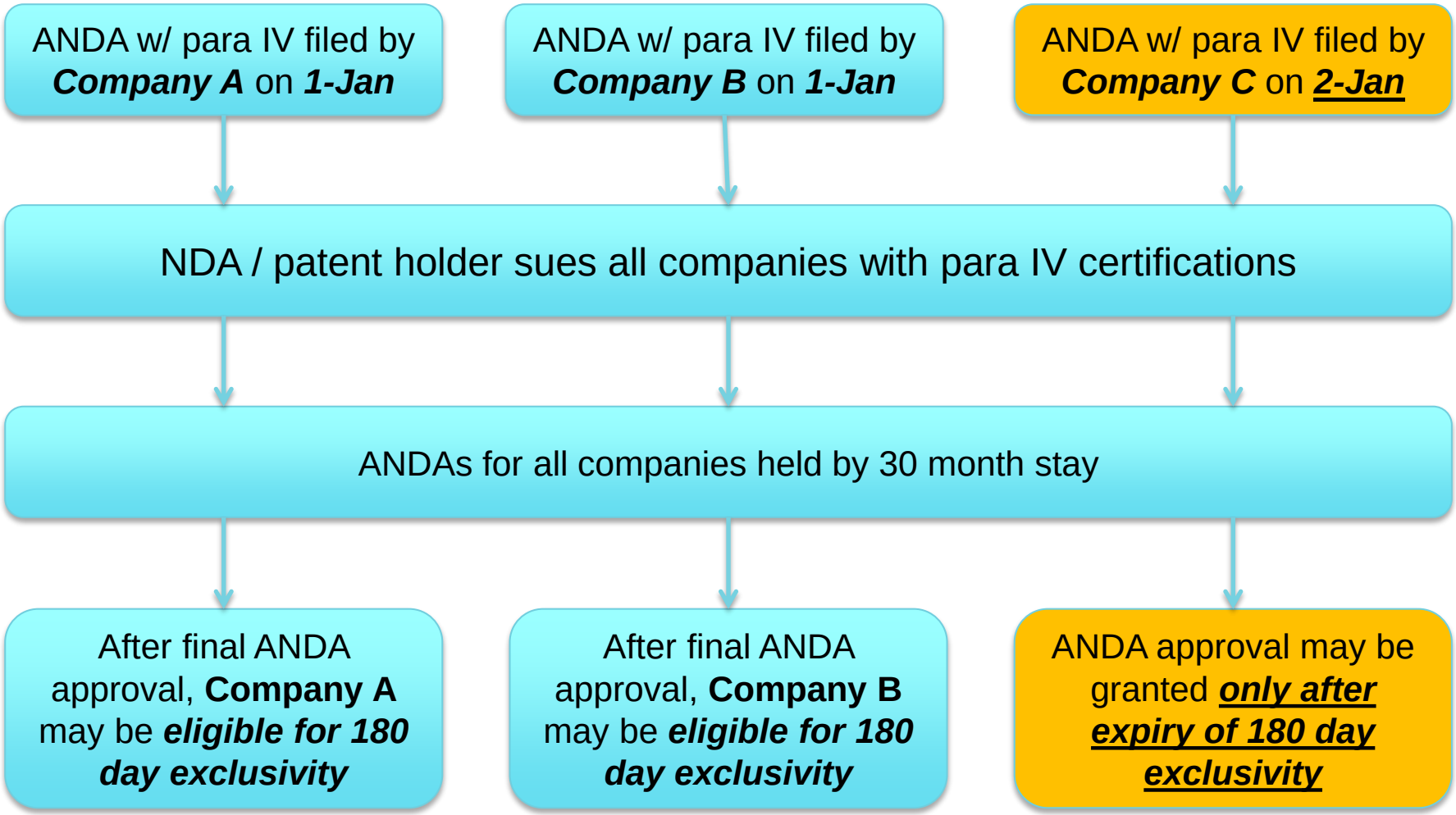
Implication → Applicants that are first-to-file are eligible for 180 days of marketing before other companies.

FDA publishes frequent updates to first-to-file para IV certifications

Paragraph IV Patent Certifications
January 31, 2018

DRUG NAME	DOSAGE FORM	STRENGTH	RLD/NDA	DATE OF SUBMISSION
Abacavir Sulfate	Tablets	300 mg	Ziagen 20977	1/28/2009
Abacavir	Oral Solution	20 mg/mL	Ziagen 20977	12/27/2012
Abacavir Sulfate, Dolutegravir and Lamivudine	Tablets	600 mg/50 mg/300 mg	Triumeq 205551	8/14/2017
Abacavir Sulfate and Lamivudine	Tablets	600 mg/300 mg	Epzicom 21652	9/27/2007
Abacavir Sulfate, Lamivudine and Zidovudine	Tablets	300 mg/150 mg/300 mg	Trizivir 21205	3/22/2011
Abiraterone Acetate	Tablets	250 mg	Zytiga 202379	4/28/2015
Abiraterone Acetate	Tablets	500 mg	Zytiga 202379	8/23/2017
Acarbose	Tablets	25 mg, 50 mg and 100 mg	Precose 20482	3/22/2005
Acetylcysteine	Injection	200 mg/mL, 30 mL vials	Acetadote 21539	4/4/2012
Acetaminophen*	Injection	1000 mg/100 mL (10 mg/mL)	Ofirmev 22450	4/7/2011
Acetaminophen	Extended-release Tablets	650 mg	Tylenol 19872	

What happens if multiple companies are first-to-file with para IV certifications on the same day?



There should only be one period of generic drug exclusivity for a given product

Complexities with patent expiry / para IV litigation

- **180-day exclusivity could be forfeited in certain scenarios[5].**
  - Examples include:
    - Failure to obtain a tentative approval in 30 months
    - Failure to market within a specified time after approval
    - Expiration of all patents with which exclusivity is associated
    - Withdrawal of the ANDA or all paragraph IV certifications
- **Terms of competitor litigation settlements not be public.**
- **Authorized generics**

Authorized Generics (AG)

- **An 'authorized generic' is an approved brand name drug without the brand name on the label.**
  - Other than that, it is the exact same drug product.
  - May be sold by the brand name company or licensed by another company.
  - NDA holder must notify FDA there will be an authorized generic.

- **There are several differences from Generic ANDA drugs:**
  - ANDA generics have the same active ingredient, route of administration, strengths, etc
  - Developed by another company other than brand.
  - Suppliers and Inactive ingredients could be different that RLD.
  - ANDA must be approved by FDA to be able to market the product.

Source:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm126389.htm

Questions

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