AN INNOVATIVE ECOSYSTEM FOR MEDICINES:
EFFECTIVE PATENT ENFORCEMENT
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Introduction

The role of innovation in the pharmaceutical sector from extending patient lives to lowering overall cost of healthcare delivery is well documented and indisputable. The discovery of new life-saving medicines is made possible by the protection of intellectual property—specifically patents. Patents are a key incentive for the innovative (pioneer) industry to allocate scarce resources in costly and time-consuming research and development (R&D). Exclusive marketing rights based on patent rights are the way pioneers recoup their R&D costs and the costs to obtain marketing approval to bring the medicine to the marketplace. On average, studies have shown that pioneer drugs lose significant sales upon the entry of generic drug with an estimated seventy-five percent (75%) lost within the first three (3) months and up to eighty percent (80%) within the first six (6) months\(^1\). Supporting the pipeline of R&D for new medicines is critical for patients around the world. At the same time, the generic drug industry is also an important part of the healthcare ecosystem. Countries around the world attempt to create balanced systems to ensure access to pioneer medicines by protecting intellectual property and to lower the cost of these medicines through the availability of generic drugs. The global necessity to stimulate pharmaceutical innovation while facilitating access to lower cost pharmaceuticals is inevitably tied together in the patent enforcement system.

The mechanisms for implementation of an effective patent enforcement system can vary; but all functioning systems share the following common characteristics:

- **Identification of Relevant Patents**: A transparent way to identify relevant patents in force, such as by listing patents that cover pioneer medicines in a central repository that is publicly available.
- **Notice of the Filing of a Generic Application(s)**: Timely notice is required to be provided to new drug application holders and/or patent holders when a generic company has started the formal process of securing regulatory approval for its product. For example, requiring the generic applicant to provide early notice to the new drug application and patent holders that it has filed an application and that it intends to market its product before expiration of patents that cover that reference new drug product.
- **Early Resolution of Patent Disputes**: Enabling patent holders to promptly initiate legal proceedings for infringement and to resolve patent disputes before generic applications are approved or marketing begins. The system allows patent holders to seek and receive stays of approval, preliminary injunctions or other provisional enforcement measures to prevent approval or marketing of generics for a reasonable period that permits resolution of patent disputes.

The underlying objectives of transparency and predictability support a functioning system. The opportunity for both the pioneer and generic company to obtain patent certainty in advance of commercial marketing or approval is critical. In the United States, a “patent linkage” system has been implemented that provides the pioneer and generic companies with the ability to enforce patents and seek earlier access of generic drugs, respectively. In addition to the United States, similar systems have been more recently implemented in other markets, including Canada and South Korea.

In 1984, U.S. Congress passed legislation—informally known as Hatch-Waxman—that created the modern day pharmaceutical industry in the United States, including an effective patent enforcement system. The patent linkage provisions in Hatch Waxman outline the process by which a generic company provides notice to the patentee of their application seeking approval of the generic version prior to expiration of the relevant patent(s), affords an opportunity for the patentee to bring a patent infringement suit, and prevents the United States Food and Drug Administration (FDA) from approving the generic drug application for a period time during the patent litigation. As a result, the patent linkage system coupled with other marketing exclusivities provided under Hatch-Waxman has resulted in the United States having one of the strongest pharmaceutical industries in the world in terms of innovation and access to generic drugs.

The U.S. pharmaceutical market is the largest in the world with sales reaching $339.7 Billion in 2013.²

Thirty four hundred (3,400) of the five thousand (5,000) globally developed new drugs are in development in the United States, an increase of 40% since 2005.³

The number of new drug application (NDA) and abbreviated new drug application (ANDA) approvals continue to increase with six hundred sixty-one (661⁴) NDA/BLAs⁵ (Biological License Applications) approved by the FDA during January 1, 2010 and January 28, 2016.

One hundred seventy-nine (179) of the six hundred sixty-one (661) new drug approvals are for new chemical entities (NCE) or novel drugs, including one (1) for a new enantiomer of a previously approved NCE (27.0%).

At the same time, due to the balance achieved by the Hatch Waxman Act,

Use of generic drugs in the United States increased from a little over eighteen percent (18.6%) of total prescriptions in 1984 prior to the passage of the legislation to eighty-six percent (86%) in 2013³ and projected to increase to ninety percent (90%) by 2020⁰.

FDA approved two thousand seven hundred sixty-five (2,765) ANDAs between January 2010 and January 28, 2016.⁸

Generics are using the patent linkage mechanism in the United States. One hundred fifty-seven (157) of the six hundred sixty one (661) NDAs are subject to patent challenges seeking market entry prior to patent expiration.

The U.S. generic pharmaceutical market accounts for 45% of the global generic market with value of $43.5 Billion in 2013 and is expected to experience double-digit (~11%) compounded annual growth rate through 2018.⁹

This paper examines effective patent enforcement systems and mechanisms adopted by several countries, including the United States, Canada, and South Korea with a particular emphasis on the modern day U.S. patent linkage system. The paper reviews U.S. history on patent linkage, clear rules of engagement; timely resolution of patent challenges through the court system, and the effectiveness of patent linkage through a review of the data from January 2010 to January 2016. In addition, the paper reviewed provisions of Hatch-Waxman that have directly contributed towards developments of new and better medicines; introduced cheaper alternatives to older medicines; contributed to a more professional regulatory agency; and created a robust pharmaceutical reimbursement system that rewards both innovation and greater manufacturing efficiencies.

² 5 Largest Markets for Pharmaceuticals, Available at http://www.fool.com/investing/general/2015/05/12/5-largest-markets-for-pharmaceuticals.aspx
³ See Medicines in the Pipeline (http://www.phrma.org/pipeline); See Also Pharmaceuticals, Small Business and IP, Available at http://sbecouncil.org/2014/07/11/pharmaceuticals-small-business-and-international-ip/
⁴ This number is based on distinct application numbers and therefore can count multiple strengths or the dosage form of the same active ingredient separately.
⁵ The inclusion of BLAs in this analysis is limited to the biological products that were approved by the FDA’s Center for Drug Evaluation and Research (CDER).
⁸ Source: Drugs@FDA found at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.
I. Background on United States Patent Linkage System

The patent linkage system finds its roots in the Drug Price Competition and Patent Term Restoration Act of 1984, also known as Hatch-Waxman.10 Drugs have been regulated in the United States since 190611, however, it was not until the passage of Hatch-Waxman in 1984 by U.S. Congress that an abbreviated pathway for generic drugs was introduced to stimulate competition and access to low cost quality generic drugs. Hatch-Waxman generally requires the FDA to withhold approval of a generic drug application (i.e., ANDA) of a previously approved NDA that is covered by certain unexpired patents. In turn, Hatch-Waxman provided the pioneer drug industry with a set of incentives to increase innovation within the U.S. pharmaceutical sector, including the opportunity to enforce their patents prior to the entry of potentially infringing generic versions.

A. Hatch-Waxman Legislative History

The road that led to Hatch-Waxman commenced with U.S. President Jimmy Carter’s domestic policy review of challenges to industrial innovation in 1978.12 One of the recommendations of the committee was the need for patent term extensions to compensate for time lost by patent applicants for their products that required prior government approval.13 This led to debates on potential legislation14 to provide such extension that resulted in the generic drug industry making its own push for legislation facilitating generic drugs. As a result, on September 24, 1984, U.S. Congress passed Hatch Waxman legislation with negotiations led by Senator Orrin Hatch (State of Utah) and now retired Congressman Henry Waxman (State of California), amongst other Congressional Representatives.

B. Hatch-Waxman Incentives for Pioneer and Generic Drug Industry Development

Under Hatch-Waxman, a set of incentives for both the pioneer and generic drug industries are provided to facilitate innovation and access. For the pioneer industry, the law provides the industry with not only patent term extensions (PTE) to compensate for lost time during the FDA regulatory process for their NDA, but also listing of patents (Listed Patents) that cover the NDA in the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book)15, regulatory marketing exclusivities and patent linkage. In turn, for the generic drug industry, Hatch-Waxman introduced an abbreviated new drug application process for generic drugs that limits the amount of data required by the FDA and provides regulatory marketing exclusivity incentive to challenge Orange Book Listed Patents for the approved new drug application (NDA) that is the referenced in the ANDA (Reference Listed Drug or RLD). The operation of the patent linkage system is intrinsically intertwined in the ANDA approval pathway that outlines the requirements and obligations of both the pioneer and generic drug applicants.

1. Abbreviated New Drug Application Pathway

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10 Public Law 98-417
13 At that time, the regulatory approval process took seven (7) to ten (10) years and most testing was done after the relevant patent was granted. This resulted in an effective duration of patent protection for many new drugs to be as low as seven (7) years. See Roche Prods., Inc. v. Bolar Pharm. Co., 733 F.2d 858, 864 (Fed. Cir. 1984).
Prior to Hatch-Waxman, all drugs were considered and regulated as “new” drugs. This required a company seeking approval for a generic drug to either repeat the costly clinical studies conducted by the pioneer drug applicant or to find and submit to the FDA literature and other published data to support safety and effectiveness findings. Under Hatch-Waxman, the ANDA approval pathway was established that makes available a shorter, streamlined pathway for generic drugs that, in comparison to the respective RLD have the same:

- Active ingredient(s);
- Route of Administration;
- Dosage Form;
- Strength; and
- Labeling.

If a generic drug meets these requirements, then under most circumstances the only clinical data that is required to support the ANDA is bioequivalence studies to show that the rate and extent of absorption of the drug are within the allowable range in comparison to the RLD. As a result, the scope of the regulatory review for approval of a generic drug application is abbreviated compared to a new drug.

**FDA Regulatory Review of Applications**

Under certain circumstances, a generic drug applicant can also file an ANDA versus a NDA for a change in the dosage form, strength, or route of administration of a new drug by submitting a petition to the FDA. If the FDA is satisfied that the generic applicant has submitted sufficient information to show that the contemplated change to the RLD does not change the pharmacological or therapeutic class, the FDA will approve the petition (Suitability Petition) and allow for the submission of ANDA with the change versus requiring the submission of a NDA. The availability of the ANDA pathway eliminated the need for costly clinical trials for generic drugs, which inhibited growth of the generic pharmaceutical sector in the United States prior to the passage of Hatch-Waxman.

2. Incentives for Development of Both New & Generic Drugs

Hatch-Waxman includes a set of incentives for both the pioneer drug and generic drug industries in order to maintain the balance of innovation and access. Following the implementation of Hatch-Waxman, a number of amendments have been made to the law to address the needs of both the pioneer and generic drug industries. The most relevant set of the provisions contained in Hatch-Waxman and subsequent amendments are identified below and discussed in detail in Appendix I.
Hatch-Waxman Incentives

New Drug Incentives

• Patent Term Extensions
• Submission of Patent Information & Prior Notice of Generic Drug Applicants Seeking Earlier Market Entry
• Patent Linkage - 30-Month Stay / Up to 42 Months for NCEs
• Regulatory Marketing Exclusivity for New Chemical Entities, New Clinical Investigations, Pediatric Studies, Qualified Infectious Disease Product & Orphan Drug Exclusivities

Generic Drug Incentives

• Developing Product Prior to Patent Expiration (Bolar Exemption)
• Ability to Challenge Patents Prior to Expiration
• Carve-Out of Method of Use Patents to Accelerate Approval
• Regulatory Market Exclusivity Incentive to Challenge Patents
• Submission of Clinical Data Limited to Bioavailability Studies- Reliance Upon Safety and Effectiveness Data

II. Operation of U.S. Patent Linkage System

In the United States, the operation of patent linkage involves clearly defined roles for the FDA, drug applicants (i.e., NDA and ANDA holders), and the Judicial System that effectively monitor and implement the system. The initiation of the system commences with the NDA holder at the time of submission of their application identifying all patents that “claim the drug or a method of use”. With respect to method of use patents, the NDA holder must also submit a description of each indication claimed by the patent, referred to as “use code narratives”. Under Hatch-Waxman, the FDA publishes all patent information related to NDAs that have been approved, including the use code narratives provided by the NDA holder, as well as the existence of any marketing exclusivity such as New Chemical Entity exclusivity in the Orange Book.

A. Listing Patents

The listing of patent and exclusivity information in the Orange Book is the initial and critical piece of the patent linkage system. For each patent listed in the Orange Book, an ANDA must make one of the following certifications that “in the opinion of the applicant and to the best of his/her knowledge, with respect to each patent which claims the drug [NDA] for which such investigations were conducted or which claims a use for such [NDA] drug for which the [ANDA] applicant is seeking approval”:

- that such patent information has not been filed by the NDA holder for listing in the Orange Book (so called, Paragraph I Certification),
- that such patent [listed in the Orange Book] has expired [at the time of filing of the ANDA] (so called, Paragraph II Certification),
- ANDA applicant is not seeking approval of its application until the date on which such patent [listed in the Orange Book] will expire (so called, Paragraph III Certification), or

An NDA Holder can also submit a patent for listing in the Orange Book following the approval of its NDA as long as the submission for listing is made to the FDA within thirty (30) days of the patent being issued by the USPTO.

16 See Example Orange Book Listing of Patents For An Approved New Drug (Salix/Valeant Pharmaceutical’s Apriso® (Mesalamine), Available at https://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=022301&Product_No=001&table1=OB_Rx

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• that such patent [listed in the Orange Book] is invalid or will not be infringed by the manufacture, use, or sale of the new [generic] drug for which the [ANDA] application is submitted (so called, **Paragraph IV Certification**).

### Patent Certifications

**Paragraph I**
- No Listed Patents

**Paragraph II**
- Listed Patent Has Expired

**Paragraph III**
- Listed Patent Will Expire On A Particular Date

**Paragraph IV**
- Patent Is Invalid Or Will Not Be Infringed By the Generic Drug For Which Approval Is Being Sought

In addition, for any “method of use” patent listed in the Orange Book for a new drug that is subject of a NDA, the generic applicant can make a statement claiming that they are not seeking approval for that method of use in the labeling of their ANDA (so called, Labeling Carve-Out or Section \textit{vii} Statement).

### B. Notice Requirements Of Generic Applicants

If the generic drug applicant submits a Paragraph III Certification to any of the patents listed in the Orange Book for the RLD, the FDA cannot approve the ANDA until the expiration of that patent. In addition, if the ANDA contains a Paragraph IV certification to any of the Listed Patent for the RLD, this triggers the potential application of Patent Linkage and Notice of the filing of the ANDA containing a Paragraph IV Certification by the generic drug applicant to the RLD and Listed Patent Holders. The application and timing of Patent Linkage are dependent on whether the generic drug applicant submits a Paragraph IV Certification in its original ANDA or if it later amends its application to contain such a certification (e.g., Change from Paragraph III to Paragraph IV Certification for a Listed Patent).

### Notice of Filing of ANDA with a Paragraph IV by Generic Applicants

**Original ANDA Containing Paragraph IV Certification**
- Within 20-Days of Receipt of Acknowledgment from the FDA that the ANDA has been accepted for filing, provide Notice of Patent Challenge and Confidential Access to ANDA Information, including basis of patent challenge to NDA and Listed Patent Holder

**Amended or Supplemented ANDA With Paragraph IV Certification for any Listed Patent**
- Provide Notice of Patent Challenge and Confidential Access to ANDA Information at time of amendment or supplement, including basis of patent challenge to NDA and Listed Patent Holder
C. Patent Infringement Suit & Automatic Stay of Generic Approval

Upon receipt of the Notice of the Patent Challenge, if the RLD or Listed Patent Holder bring a suit for patent infringement within forty-five (45) days of receipt of the Notice of Patent Challenge from the ANDA holder, the FDA is prohibited from approving the ANDA until thirty (30) months from the date of receipt of the Notice of Patent Challenge by the RLD/Listed Patent Holder (known as the Automatic Stay), unless a District Court decides that the patent is invalid, not infringed or unenforceable. In these circumstances, the FDA can approve the ANDA on the date of the court decision or the date of the settlement or consent decree entered by the court. The Automatic Stay can also be extended or reduced at the discretion of the District Court entering an order at the request of either party because the other party failed to reasonably cooperate in expediting the patent litigation.

Availability & Implementation of Automatic Stay of Approval

If the NDA or Listed Patent Holder does not bring a patent infringement suit within the statutory forty-five (45) days from the date of receipt of the Notice, the FDA can approve the ANDA immediately upon completion of their review of the ANDA. On the other hand, if before the expiration of the Automatic Stay, the District Court determines that the ANDA infringes the patent(s) in suit, the FDA cannot approve the ANDA until the patent(s) expires or there is a settlement or consent decree entered. If the generic drug applicant appeals the adverse ruling to the Court of Appeals for the Federal Circuit (Federal Circuit), the FDA cannot approve the ANDA until either the decision is made by the Federal Circuit that the ANDA does not infringe or until the patent expires.

Notably, one of the major changes made to the Patent Linkage system in the United States since the passage of Hatch-Waxman was to limit the number of Automatic Stays through passage of the Medicare Modernization Act of 2003 (MMA) and ensuing implementing Guidance by the FDA. Prior to the

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18 See Federal Courts Improvement Act of 1982, Public Law 97-164
19 Public Law 108-173
20 See Listed Drugs, 30-Month Stays, and Approval of ANDAs and 505(b)(2) Applications Under Hatch-Waxman, as Amended by the Medicare Prescription Drug Improvement, and Modernization Act of 2003,
MMA, following approval of its NDA, an applicant at any time could submit a new patent to the FDA to list in the Orange Book within thirty (30) days of issuance of the patent by the United States Patent and Trademark Office (PTO). This later listed patent by the FDA in the Orange Book required all new and pending ANDA holders to submit a Patent Certification to this new patent that could trigger another Automatic Stay. Under the MMA, a pending ANDA holder that had previously submitted a Paragraph IV Certification cannot be subject to another Automatic Stay irrespective of whether or not they were subject of a previous Automatic Stay. However, an exception applies to an ANDA holder that after filing its ANDA with the original patent statements, including a Paragraph IV Certification to at least one Listed Patent and a Paragraph III Certification to another Listed Patent changes its previously submitted Paragraph III patent certification to a Paragraph IV Certification. Under this latter scenario, the ANDA can be subject of an additional Automatic Stay.

Another nuance to the Automatic Stay applies to NDAs that are deemed by the FDA to contain a NCE. In general, an ANDA holder is prohibited from filing its application seeking approval of a generic version of the NDA containing a NCE until the expiration of the NCE exclusivity period (i.e., five (5) years). The one exception to this rule is if the generic applicant intends on challenging one of the Listed Patents for the NCE drug in which case the ANDA can be filed one (1) year prior to the expiration of the NCE exclusivity (NCE-1 Year, i.e. NCE minus one year). If the NDA or Patent Holder brings a patent infringement action during the one (1) year starting four (4) years after the date of approval of the NDA containing the NCE, the Automatic Stay is extended by such amount of time (if any) that is required for seven and one-half (7 ½) years to have elapsed from the date of approval of the NDA containing the NCE.

Stakeholder Roles in U.S. Patent Linkage System

21 The PTO does not play a direct role in the implementation of the patent linkage system.

III. January 2010 to January 28, 2016 Data on Filings in the United States

1. NDA and ANDA Filings

In the United States, the filing of drug applications, NDA or ANDA, is confidential and not publicly disclosed by the FDA. However, the FDA has on occasion disclosed aggregate data on the number of annual filings. For example, in the Prescription Drug User Fee Act (PDUFA) Performance Reports, the FDA disclosed that in fiscal year (FY) 2010, the FDA received one hundred three (103) NDA and BLA original applications, one hundred one (101) in FY 2011, one hundred thirty (130) in FY 2012, one hundred thirty-eight (138) in FY 2013 and one hundred thirty-two (132) in FY 2014 for a total of six hundred four (604) or approximately one hundred twenty-one (121) annually during this time period.

<table>
<thead>
<tr>
<th>Year</th>
<th>FY 2010</th>
<th>FY 2011</th>
<th>FY 2012</th>
<th>FY 2013</th>
<th>FY 2014</th>
<th>Total</th>
<th>Average per FY</th>
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<tr>
<td>NDA/BLA Filings (FY 2010 to FY 2014)</td>
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</tr>
<tr>
<td>Number of NDAs &amp; BLAs Received by FDA</td>
<td>103</td>
<td>101</td>
<td>130</td>
<td>138</td>
<td>132</td>
<td>604</td>
<td>120.8</td>
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</table>

In addition, public data is available from the FDA on the number of NCEs that have been filed during the Calendar Years (CY) 2010 to 2015. According to this data, the FDA received, in CY 2010 twenty-three (23) NCEs, forty-one (41) in CY 2011, forty-one (41) in CY 2012, thirty-six (36) in CY 2013, forty-one (41) in CY 2014, and forty (40) in CY 2015 for a total of two hundred twenty-two (222) or approximately thirty-seven (37) annually during this time period.

<table>
<thead>
<tr>
<th>Year</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>Total</th>
<th>Average per CY</th>
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<tbody>
<tr>
<td>NCE Filings (CY 2010 to CY 2015)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Number of NCEs Filed</td>
<td>23</td>
<td>41</td>
<td>41</td>
<td>36</td>
<td>41</td>
<td>40</td>
<td>37</td>
</tr>
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</table>

With respect to the filing of generic drug applications (i.e., ANDAs), during January 2010 to December 2015, the data available is limited to the information provided under Performance Reviews of the Generic Drug User Fee Act (GDUFA) and FDA Activity Report with first set of data reported in 2013. According to the GDUFADA and Activity Report data, in CY 2013, there were nine hundred ninety-eight (998) ANDAs filed, one thousand two hundred sixty-nine (1,269) filed in CY 2014 and six hundred seventy-six (676) in CY 2015 for a total of two thousand nine hundred forty-three (2,943) during this three (3) year period or approximately nine hundred eighty-one (981) annually during this time period.

24 See FY 2014 GDUFA Performance Report Available at, http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/UCM451179.pdf; See Also, FDA Activity Report, Available at
ANDA Filings (CY 2013 to CY 2015)\textsuperscript{25}

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<th>2015</th>
<th>Total</th>
<th>Average</th>
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<td>Number of ANDAs filed</td>
<td>998</td>
<td>1,269</td>
<td>676</td>
<td>2,943</td>
<td>981</td>
</tr>
</tbody>
</table>

Number of NDA/BLA, NCE & ANDA Filings

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{Number of NDA/BLA, NCE & ANDA Filings}
\end{figure}

\textsuperscript{25} There are a number of factors that impact the number of annual ANDA filings, including, expiration of patents of new drugs, the cost of filing and maintaining an application under GDUFA for new drugs that are saturated by generic drugs to generic companies looking to invest their resources in more difficult to manufacture products that require more development time.

2. Patent Challenges

Similar to NDA and ANDA filing data, the FDA does not maintain a full, comprehensive public list of patent challenges to NDAs. However, the agency under pressure from industry has started to maintain data on the existence of a patent challenge to a NDA. According to this data, between January 1, 2010 and January 28, 2016, there have been a total of three hundred sixty-four (364) patent challenges by ANDA applicants involving two hundred ninety-nine (299) NDAs during this timeframe with one hundred fifty-seven (157) of these patent challenges to NDAs that were approved during this period. So, out of the six hundred sixty-one (661) new drug applications approved between January 2010 and January 28, 2016, approximately twenty-four percent (23.7%) are subject of an ANDA containing a Paragraph IV Certification (i.e., patent challenge).

3. ANDA Denials or Delays

As noted previously, between January 1, 2010 and January 28, 2016, there have been approximately six hundred sixty-one (661) NDA/BLAs approved by the FDA or approximately one hundred thirty (~130) on an annual basis. Out of these six hundred sixty-one (661) approvals, generic drug companies have already submitted an ANDA containing a Paragraph IV Certification for one hundred fifty-seven (157) of these NDAs. Assuming the RLD or Patent Holder has filed a patent infringement suit for these one hundred fifty-seven (157) ANDAs during the statutory forty-five (45) days, the subject ANDA could not be approved for thirty (30) or forty-two (42) months in light of the Automatic Stay provisions. For these one hundred fifty-seven (157) ANDAs containing a Paragraph IV Certification, there are five (5) ANDAs or approximately three percent (3.18%) that have received a Tentative Approval from the FDA despite the Automatic Stay having expired and presumably not extended by a Court. In addition, fifteen (15) of these ANDAs or approximately nine and one-half percent (9.55%) have neither a Tentative nor Final Approval according to publically available information. Consequently, out of the one hundred fifty-seven (157) ANDAs containing a Paragraph IV Certification, twenty (20) or approximately thirteen percent (12.7%) should be eligible for Final Approval, but are most likely delayed due to the ANDA not being ready for approval from a regulatory perspective. Most importantly, out of these one hundred fifty-seven (157) ANDAs, thirty-eight (38) or approximately twenty-four percent (23.7%) have already received Final Approval with the remainder presumably still under an Automatic Stay period that has not been shortened by the relevant District Court.

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4. Patent Life

In reviewing patent information that has been listed in the Orange Book for the six hundred sixty-one (661) new drug applications that contain an NCE and that were approved by the FDA during January 1, 2010 and January 28, 2016, average of eleven and a quarter (11.25) years of patent life were left on the Listed Patents at the time of approval of the NDA.

5. Patent Term Extensions

Out of the six hundred sixty-one (661) NDA/BLAs that were approved by the FDA between January 1, 2010 and January 28, 2016, thirty-one (31) Listed Patents covering these drug applications have been approved for patent term extension, which represents a little over four and one-half percent (4.68%)\(^{27}\). Note, this does not include any pending requests for extension, but does include one (1) interim extension for one (1) year and six (6) Listed Patents that cover more than one application. The average length of the patent term extension was approximately one thousand one hundred forty-one days (1,140.87) or approximately 3.12 years of an extension. The range of the patent extension was from seventy-two (72) days to the maximum five (5) years.

\(^{27}\) Source: Drugs@FDA; See Also, www.regulations.gov
In addition to the January 1, 2010 and January 28, 2016 Approved NDAs, there are thirty-seven (37) NDAs that are identified on FDA’s Paragraph IV list during this same time-frame that received patent extensions. The range of these patent term extensions ranged from eighteen (18) days to the maximum five (5) years with an average of one thousand two hundred thirty-eight (1,238.56) days or 3.39 years.

IV. Patent Enforcement Systems and Mechanisms in Key Markets

Countries and regions around the world have evolved different systems for protecting pharmaceutical patents in their own jurisdictions, with varying effectiveness that in turn shapes the growth and development of their indigenous pharmaceutical industry. In some instances, the pharmaceutical industry has its roots in the 19th century or before, while in others, pharmaceutical companies have only recently set up manufacturing and/or R&D in the country. Finally, a major factor in the shape and success of the domestic pharmaceutical industry is the system for pharmaceutical reimbursement in that particular country.

A. Canada

Canada’s patent linkage system is contained in the Patented Medicines (Notice of Compliance) Regulations (“PM (NOC)”)

28, which aim to prevent patent infringement of a potentially infringing generic drug by prohibiting its notice of compliance (NOC) (i.e., drug approval) by the Minister of Health (MoH). The Canadian PM (NOC) system has a lot of similarities to the U.S. Hatch-Waxman Patent Linkage System, including:

- Holder of the New Drug Submission (NDS) (e.g., NDA) must submit relevant patent information covering their new drug to the MoH
- A Patent Register (Similar to the Orange Book) is maintained for all approved drug products in the country
- At the time of the filing of the subsequent or second (e.g., generic) application that references a drug listed in the Patent Register with an associated patent, the subsequent/second applicant must submit a declaration with respect to each listed patent noting:
  - Accepts that Notice of Compliance will not be issued until the patent expires; or
  - Makes one of the following four (4) allegations (Notice of Allegation):
    - Person who submitted the patent for registration in the Patent Register made a false statement with respect to being the owner or having the consent of the owner for the patent;
    - The patent has expired;
    - The patent is not valid; or
    - The patent will not be infringed by the generic product
- The Notice of Allegation with information on its generic drug (e.g., formulation, use, etc.) and legal and factual basis for the allegation must be provided to the Holder of the NDS on or after the submission of its application
- The NDS Holder within forty-five (45) days of receipt of Notice of Allegation can file an action in Court prohibiting MoH from approving the generic drug until expiration of the patent(s) and within forty-five (45) days serve the MoH to notify them of the action filed in court
- As a result, the MoH is prohibited from issuing a NOC to the generic applicant up to twenty-four (24) months during which time the court decides on the merits of the case (e.g., infringement or validity).
- The twenty-four (24) month time frame can be extended or shortened if the parties consent or if the court finds either party has not reasonably cooperated in the proceedings.

28 Patented Medicines Regulations (SOR/93-133) (Last Amended, June 19, 2015)
In addition, similar to the U.S. Federal Trade Commission (FTC), Canada has taken the position that it will scrutinize patent settlements involving so-called reverse payments\(^{29}\) (See Appendix I for Discussion on Anti-Trust).

B. Republic of Korea (South Korea)

The pharmaceutical industry in South Korea is relatively young with a primary emphasis of the domestic industry on the manufacturing and marketing of generic pharmaceuticals for the local market. The pioneer industry in South Korea is still nascent with few companies having invested in the development of new products, whether for the local or export markets. More recently, the Korean government has begun to encourage local firms to develop export markets for their pharmaceutical products, particularly pioneer products. In recognition of the role of valuing innovation in pharmaceutical reimbursement, the government has instituted a number of reforms to make investment in innovation more attractive. Notably, some of these reforms were established as part of the U.S.-Korea Free Trade Agreement, finalized in 2012.

The Patent Approval Linkage System (PALS) is a relatively new addition to Korea’s Pharmaceutical Affairs Act, with the initial implementation beginning in 2012, and full implementation in March 2015. As such, South Korea experience with its patent linkage regulations is limited. Nevertheless, in several ways, the Korean PALS is modeled on the U.S. patent linkage system.

- Similar to the U.S. system, pioneers who have received marketing approval from the Korean Ministry of Food and Drug Safety (MFDS) must notify within thirty (30)-days which patents are associated with their products\(^{30}\).
- When a generic applicant applies for marketing approval in Korea, the generic applicant must make one of the following six (6) certifications for each patent listed in the so-called Green List:
  - The patent has already expired (Item 1 Certification)
  - Not seeking marketing until after the patent has expired (Item 2 Certification)
  - The patent owner and patent listing entity have consented to waive the generic applicant’s notice obligations (Item 3 Certification)
  - The Korean Intellectual Property Tribunal or a court has invalidated the listed patent or the generic drug for which marketing approval is being sought falls outside the scope of the listed patent (Item 4 Certification)
  - The listed patent is unrelated to the generic drug for which marketing approval is being sought (Item 5 Certification)
  - The listed patent is invalid or otherwise would not be infringed (Item 6 Certification)
- The generic applicant must inform the patent holder within twenty (20)-days of the application date if the applicant is making an Item 6 Certification (Patent Challenge Notice)
- The patent owner may request a stay against generic drug sales to the Minister of MFDS within 45 days after receiving the Patent Challenge Notice (Patent Holder must first file a patent infringement action in court)


\(^{30}\) However, the MFDS then takes the additional step of validating those patents listed by the innovator for relevance, and may choose to delete patents if certain criteria are not met. Third parties, such as generic pharmaceutical companies, are also afforded the opportunity to submit their opinions. In addition, pioneers may appeal MFDS decisions regarding which patents are listed via the Patent Approval Linkage Tribunal (Tribunal) within MFDS. Only after approval by the MFDS are such patents listed in the Green List (similar to FDA’s Orange Book).
Once granted, the delay will be effective for only nine (9) months from the date of notification and most importantly does not prevent approval of the generic drug. Instead, it prevents sales of the generic drug.

Also, similar to the United States, the Korean system has an incentive for generic pharmaceutical companies to apply as early as possible for marketing approval. First-to-file applicants may receive up to nine (9) months of marketing exclusivity if they are:

- First to obtain a favorable court decision or judgment of patent invalidity or non-infringement\(^{31}\);
- Obtain a favorable court decision within nine (9) months from the date of receipt of the Patent Challenge Notice.

In summary, there are several similar provisions to the U.S. system such as providing notice to the patent and new drug application holder, while there are also key differences as only the sales being prohibited during an automatic stay period versus the approval of the generic drug product per se.

V. Available Models & Options for China

Over the years, China has become the top supplier of active pharmaceutical ingredients (APIs) for exports to the United States and other market. The majority of these APIs are used by generic pharmaceutical companies in finished dosage formulation (FDFs) marketed in developed countries such as the United States, Canada, etc. The API and generic FDF manufacturers have dominated the domestic Chinese pharmaceutical market with a disproportionately low number of innovative pharmaceuticals developed by domestic Chinese companies despite the significant investments made by the government. As noted in this report, the development of innovative medicines requires not only resources, but also a pro-innovative ecosystem that values the availability and enforceability of patents. Without a system that affords pioneer companies with a timely opportunity to enforce their patents against potentially infringing generic versions of their new drugs, the incentive to invest in R&D of new drugs is nonexistent. This leads industry to opt for the easier, short term success route of generic drug development.

If China does implement a patent enforcement mechanism for the pharmaceutical sector, there are several models that have been outlined in this Report that can form the basis for a Chinese system. The basic tenants of the system should include: (i) listing of patents by the pioneer companies; (ii) early notice of a generic applicant seeking approval prior to expiration of the relevant patents covering the pioneer’s new drug; (iii) opportunity for the pioneer company to seek judicial opinion on the validity and enforceability of their patents; and (iv) the SFDA withholding approval for a certain period of time while the pioneer and generic applicant seek patent certainty.

VI. Conclusion

The United States market intrinsically ties the contribution of patent linkage and other incentives outlined in Hatch-Waxman to the growth of its pioneer and generic pharmaceutical industries. This is evident by the continued increase in filing of new drugs co-existing with an increasing generic substitution rate. A vital component of the U.S. system is its patent enforcement system and mechanism that is commonly referred to as patent linkage. The essential elements of this patent linkage system include clear rules of engagement for both pioneer and generic applicants, timely resolution of patent challenges through the court system, incentives to both the pioneer and generic pharmaceutical companies to develop new, better medicines while introducing cheaper alternatives to older medicines, and an administrative role of the regulator (i.e., FDA) to implement the system.

As a result, the Hatch-Waxman patent linkage system coupled with incentives and exclusivities provided to pioneer and generic companies have directly led to the U.S. pharmaceutical industry being the single

\(^{31}\) Under the March 3, 2015 Amendments, a generic application that challenges a listed patent within fourteen (14) days of the initial generic applicant may also be eligible for exclusivity.
largest in the world in terms of value. In addition, the U.S. pharmaceutical market has a generic substitution rate of over eighty percent (80%) in comparison to less than twenty percent (20%) during the first year of implementation of Hatch-Waxman. Most importantly, de-risking the potential exposure to patent infringement damages by the generic industry has benefited the generic industry. Providing a path for pioneer companies to prevent infringing generic versions to be commercially marketed that can overnight destroy the entire value of their drug, pioneer industries have benefited from the patent linkage system.

The United States is not the only market that has implemented a patent enforcement mechanism that protects the value of news drugs by pioneer companies. Both Canada and South Korea have also implemented systems that provide mechanisms that have many common attributes to the U.S. system in balancing the interests of both the pioneer and generic drug applicants. In addition, markets such as Japan and European Union have also provided other types of mechanisms (e.g., preliminary injunctions) that afford similar opportunities for industry. Overall, the common objective of valuing innovation, the role of patents in innovation, providing patent certainty to generic applicants, transparency and predictability have been successfully implemented in markets around the world.

### Common Patent Enforcement Elements

<table>
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<tr>
<th>Country</th>
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<tr>
<td><strong>Listed Patents by Innovator</strong></td>
<td>Patent Register</td>
<td>Green List</td>
<td>Orange Book</td>
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<tr>
<td><strong>Ability to Challenge Listed Patents</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Notice by Generic Applicant</strong></td>
<td>Notice of Allegation</td>
<td>Patent Challenge Notice within 20 days of application</td>
<td>Notice of Challenge within 20 days of application</td>
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<tr>
<td><strong>Automatic Stays</strong></td>
<td>24 Months</td>
<td>9 Months</td>
<td>30 Months or 7 ½ Years From Date of Approval of New Drug for NCEs</td>
</tr>
<tr>
<td><strong>Ability of Pioneer to File Suit To Avail Automatic Stay</strong></td>
<td>Within 45 Days of Receipt of Notice of Allegation</td>
<td>Within 45 Days of Receipt of Patent Challenge Notice</td>
<td>Within 45 Days of Receipt of Notice of Challenge</td>
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Appendix I

New Drug Incentives

I. Patent Term Extension (PTE)

With the passage of Hatch-Waxman, patent and NDA applicants became eligible for PTE to recover part of the patent life lost during the early years of their patent(s) because the new drug covered by the patent could not be marketed without prior approval from the FDA. The request for an extension of the patent must be made to the United States Patent & Trademark Office (PTO) within sixty (60)-days of receiving approval from the FDA for commercial marketing of the new drug. The term of a patent can only be extended up to a maximum of five (5) years with final expiration of the patent not extending beyond fourteen (14) years after FDA approval of the new drug. In general, only one (1) patent term extension is available for each new drug product that is subject to regulatory review and that has not been previously approved. If there are multiple patent term extension applications for the same new drug product, the applicant must choose which patent to extend. If the applicant does not choose, the default is to extend the patent that expires earlier. In addition, if one (1) patent covers multiple new drug products that are subject to regulatory review, only one (1) extension of the patent is possible.

The PTE for a patent is calculated by taking the sum of one-half (1/2) of the time in the testing phase of the drug (e.g., Investigational New Drug Phase), plus all the time it takes FDA to review and approve the NDA. However, the applicable extension period is reduced if any of this period occurred prior to the grant of the patent or if the patent applicant is deemed not to have acted with due diligence during clinical testing and regulatory review phases.

PTE Eligibility & Methodology

Eligibility Requirements

- Patent claims product, method of use, or method of manufacturing
- Patent has not expired
- Patent has not been previously extended
- Product claimed is subject of FDA review prior to approval/use
- Product approval is the first permitted commercial marketing of product
- Only 1 patent extension per product
- Applicant submits extension request to USPTO within 60-days of approval of the product from the FDA

Extension Calculation

- 1/2 of Testing Period + Approval Period
  - Testing Period: Date Investigation New Drug Application (IND) becomes effective until NDA is filed
  - Approval Period: Date NDA is filed with FDA
- Maximum of 5 Year Extension
- Cannot result in remaining patent term to be more than 14 years

32 If the patent that is eligible for an extension also claims other products in addition to the FDA approved drug, the patent expires with the original expiration date of the patent with respect to covering the other product.

In 1993\textsuperscript{34}, the availability of PTE was extended to allow for an interim extension of a patent if the applicant reasonably believed that the patent covering its drug product would expire prior to its NDA being approved by the FDA. The patent holder beginning six (6) months prior to the original patent expiration date and fifteen (15) days prior to the expiration date can make a request for an interim extension.

II. Submission of Patent Information & Prior Notice of Certain ANDAs

In order to ensure that NDA and Patent Holders (the two can be different) are afforded an opportunity to protect their invention, Hatch-Waxman requires NDA applicants to identify and submit to the FDA a list of all relevant patents that claim the drug or method of use. However, the FDA does not permit the submission of certain patents such as manufacturing or process patents\textsuperscript{35}. The submission of patent information covering the NDA typically occurs at the time of the filing of the application (i.e., NDA) and/or during the regulatory review of the application. However, there are instances where a new patent is issued following approval of the NDA and submitted by the NDA Holder to the FDA. In addition, for method of use patents, the NDA Holder must submit to the FDA a description of each indication covered by the patent. These descriptions of indications are referred to as “use code narratives”. In turn, the FDA publishes the patent information, including use code narratives and/or any patent term extensions granted by the United States Patent and Trademark Office (USPTO) in the Orange Book. The patent information listed in the Orange Book by the FDA for each approved NDA is informally referred to as the Listed Patent(s).

Notably, the FDA does not independently verify the patent information submitted by the NDA applicant (e.g., use code narratives). As discussed in further detail below (See Operation of Patent Linkage), if a generic drug applicant\textsuperscript{36} challenges the validity, non-infringement or unenforceability of any of the Listed Patents covering the subject RLD, the ANDA holder has to provide notice of its filing of the ANDA and an offer to access of confidential information of its ANDA (Notice) to the NDA and Patent Holder\textsuperscript{37}. This effectively provides advance notice to the NDA/RLD and Patent holder(s) that a generic applicant is seeking approval from the FDA of a generic version of its covered drug prior to the expiration of any of the Listed Patents in the Orange Book. Upon receiving Notice, if the NDA and/or Patent Holder file a patent infringement action within the statutory forty-five (45) days of receipt of the Notice, the FDA is precluded from granting Final Approval to that ANDA for thirty (30) months and, under certain circumstances, either a shorter or longer period (Automatic Stay).

III. Automatic Stay

Upon receiving Notice from an ANDA holder, the NDA or Patent Holder of the new drug referenced in the ANDA, which is typically referred to as the RLD, can file a patent infringement action within the statutory forty-five (45)-days of receiving notice that will trigger an Automatic Stay of Approval during which time the FDA cannot approve the generic drug application (i.e., ANDA)\textsuperscript{38}. If the RLD contains a new chemical entity (NCE) or new molecular entity (NME), the effective Automatic Stay is extended to seven and a half (7-1/2) years from the date of approval of the NDA if a patent challenge is brought between forty-eight

\textsuperscript{34} Public Law 103-179, Section 5

\textsuperscript{35} See Orange Book Preface, 34\textsuperscript{th} Edition, Available at \url{http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm}; See Also, FDA Form 3542, Available at \url{http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048345.pdf}

\textsuperscript{36} In addition to generic drug applicants submitting an ANDA, an applicant can also seek approval of a drug by submitting a so-called Section 505(b)(2) application that also triggers the same patent certification, notice and automatic stay provisions as a filing under Section 505(j) / ANDA.

\textsuperscript{37} For non-Orange Book listed patents, generic companies will typically obtain Freedom to Practice Opinions. Also, there is nothing that precludes the NDA or Patent Owner from challenging a generic application for these non-listed patents.

\textsuperscript{38} The NDA or Patent Holder are not restricted from filing a patent infringement suit within the statutory forty-five (45) days, however in order to avail the Automatic Stay of Approval, the suit must be brought within the statutory period.
(48)-months and five (5) years after NDA approval. The Automatic Stay can end earlier if there is a favorable District Court decision finding the relevant patent(s) invalid, not infringed or unenforceable. In all cases, prior to the issuance of a decision, the U.S. District Court has the discretion to reduce or lengthen the Automatic Stay if either party is not reasonably cooperating to expedite the patent litigation proceedings. Notably, the only patents that can form the basis for the Automatic Stay are the patents that were listed in the Orange Book at the time of the filing of the ANDA. As a result, typically there is only one (1) Automatic Stay applicable to the subject ANDA applicant, unless the ANDA applicant did not originally challenge all of the Listed Patents for the RLD at the time of filing (i.e., submitted a Paragraph III Certification to one of the Listed Patents and Paragraph IV to another Listed Patent) the ANDA and subsequently changes its Paragraph III Certification to a Paragraph IV Certification.

IV. New Chemical Entity Exclusivity

If a NDA holder submits an application seeking approval from the FDA for a drug that contains an active ingredient that has not been previously approved after September 24, 1984 (i.e, since passage of Hatch-Waxman), and for which clinical investigations were conducted (e.g., clinical trials), an ANDA that references such RLD is precluded from being filed with the FDA until the expiration of five (5) years from the date of approval of the new drug. However, if the ANDA contains a patent challenge to any of the Listed Patents for the RLD containing a NCE, the ANDA can be filed forty-eight (48) months after the date of approval of the RLD. If there are no patents listed for the RLD containing a NCE, the ANDA cannot be filed until after the expiration of the five (5) year NCE exclusivity.

In order to incentivize innovation further, in 2007, U.S. Congress amended Hatch-Waxman with the passage of the Food and Drugs Administration Amendments Act of 2007 (2007 FDAAA), which was reauthorized by the FDA Safety and Innovation Act of 2012 (2012 FDASIA). Under the 2007 FDAAA and reauthorized in 2012 FDASIA, the eligibility for five (5) year NCE exclusivity was expanded to include non-racemic drugs that contain as an active ingredient a single enantiomer that was contained in a racemic drug that was previously approved by the FDA in another application (e.g., NDA). This effectively incentivizes industry to continue to isolate and test the purity of enantiomers that could eventually be developed into drugs. For example, products developed prior to this change in law such as Clarinex® (loratadine to desloratadine) and Xyzal® (cetirizine to levocetirizine) may have been eligible for this additional five (5) year exclusivity.

However, the NDA applicant of a non-racemic drug must meet several conditions in order to receive the five (5) year NCE exclusivity, including, but not limited to, the application including 1) full reports of new clinical investigations (NCI) other than bioavailability studies that are necessary for approval, 2) does not rely upon previously submitted NCIs, and 3) the condition of use is not in the same therapeutic category as the previously approved racemic drug or in another enantiomer.

On October 10, 2014, the FDA also issued Guidance for Industry – New Chemical Entity Exclusivity – Determination for Certain Fixed Dose Combination (FDC) Drug Products that prospectively awards the five (5) year NCE exclusivity for FDCs that contain a NCE and a previously approved active ingredient. This effectively incentivizes pioneer companies to develop new drugs that may contain as one of the active ingredients that has been previously approved, but not in the same combination with marketing exclusivity. For both new drugs, including eligible non-racemic new drugs, and FDCs containing a NCE, if an ANDA...

39 In the interpreting regulations - 21 CFR §314.08(a) – active ingredient is generally defined as an active moiety.
40 Public Law 110-85
41 Public Law 112-144
42 In short, enantiomers are stereoisomers that are non-superimposable complete mirror images of one another. Enantiomers may be either “right-handed” or “left-handed” and a racemic mixture is one that has equal amounts of “left- and right-handed” enantiomers of a particular chiral molecule.
43 Available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm386685.pdf
contains a patent challenge, then the generic applicant can submit their ANDA for the RLD beginning forty-eight (48) months after the date of approval of the RLD. However, if the RLD Holder files a patent infringement action during the one (1) year period beginning forty-eight (48) months after date of approval of the RLD, the FDA is precluded from approving the ANDA until seven and one-half (7½) years have elapsed from the date of approval of the RLD.

V. New Clinical Investigation (NCI) Exclusivity

Under Hatch-Waxman, the FDA can also award three (3) years of marketing exclusivity to NDA holders for drugs that contain active ingredients that have been previously approved in another application after September 24, 1984 and that contain reports of NCIs (other than bioavailability studies) that are essential to the approval of the new drug. In contrast to the NCE exclusivity, the NCI exclusivity does not preclude a generic applicant that is referencing such RLD from submitting their respective ANDA; however, the FDA is precluded from approving the ANDA for three (3) years for the protected change. Some of the most common uses and applications of the NCI exclusivity are the approval of new indications and dosage forms (e.g., Nexium IV for New Indication Exclusivity (I-679)\(^44\); Zomig – ZMT for New Formulation (Orally Disintegrating Tablets)\(^45\).

VI. Pediatric Exclusivity

In November 1997, in light of lack of information on use of drugs by the pediatric population (i.e., age birth to sixteen (16) years old), U.S. Congress passed the FDA Modernization Act (FDAMA)\(^46\), which introduced the concept of pediatric exclusivity for manufacturers voluntarily conducting pediatric studies on their drugs. The pediatric exclusivity provided for a six (6) month add-on to unexpired periods of patent and non-patent exclusivities listed in the Orange Book for a RLD. The law initially had a sunset of five (5) years on January 1, 2002, but on January 4, 2002, U.S. Congress passed the Best Pharmaceuticals for Children Act that reauthorized the pediatric provisions for another five (5) years until it was made a permanent feature in 2012 with the passage of the FDA Safety and Innovation Act (FDASIA). In addition to making permanent the pediatric exclusivity provisions contained in the BPCA, FDAISA also made permanent the Pediatric Research Equity Act of 2003 (PREA 2003) that establishes requirements for pediatric assessments of drugs\(^47\).


\(^46\) Public Law 105-115

\(^47\) Notably, U.S. Congress passed PREA 2003 on December 8, 2003 following the District Court for the District of Columbia striking down FDA’s promulgation of the “Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients” (Pediatric Rule of 1998) that came into effect in April 1999 (See Ass’n of American Physicians and Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204 (D.D.C. 2002). The Pediatric Rule of 1998 had made pediatric studies mandatory and potentially applicable to previously approved drugs.
VII. Qualified Infectious Disease Product (QIDP) Exclusivity

Under Title VII of FDASIA (Generating Antibiotic Incentives Now), at the time of approval of the NDA, the FDA may also grant an additional five (5) years exclusivity to certain existing exclusivity periods covering the NDA (e.g., NCEs, NCIs, Pediatric) for products that have been granted a QIDP designation. For example, a new drug containing a NCE that is eligible for five (5) years of exclusivity may be granted an additional five (5) years for a total of ten (10) years of exclusivity if it is granted QIDP status at the time of approval. A QIDP is defined as “an antibacterial or antifungal drug for human use intended to treat serious or life threatening infections” including those caused by antibiotic or antifungal resistant pathogens, novel or emerging infectious pathogens, or “qualifying pathogens”. A qualifying pathogen is defined as a pathogen identified and listed by the FDA that has the potential to pose a serious threat to public health, such as “multi-drug resistant tuberculosis” amongst others. In identifying and listing a pathogen, the FDA takes into consideration multiple factors, including:

- The impact on the public health due to the drug-resistant organism in humans;
- The rate of growth of the drug-resistant organism;
- The increase in resistance rates; and
- The morbidity and mortality in humans

In addition, the FDA is required to consult with experts in infectious diseases and antibiotic resistance in updating the list of pathogens.

VIII. Orphan Drug Exclusivity

Prior to the passage of Hatch Waxman, the Orphan Drug Act was passed in 1983 by U.S. Congress that granted drugs that treat a disease or condition that affects less than: (i) 200,000 people in the United States; or (ii) for which it is unlikely that U.S. sales of the drug will recoup its development costs, marketing exclusivity. The policy objective of this exclusivity is to encourage continued testing and marketing of products for rare diseases for which no current therapy exists or the product will significantly improve existing therapy. Under this policy, a previously approved drug product can be eligible for the exclusivity under certain circumstances. This marketing exclusivity is for seven (7) years that covers the “condition of approved use” in treating the specific rare disease or condition during which time no subsequent drug application can be approved for the same rare disease or condition.

Generic Drug Incentives

I. Bolar Exemption

In exchange for the PTE provisions contained in Hatch-Waxman, the legislation also included language that was added to the U.S. Patent Code on September 24, 1984, which provided that it was not “an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention ... solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use or sale of drugs or veterinary biological products.” This has become known as the Bolar Exemption that overruled a previous Federal Circuit court ruling. Effectively, for purposes of submission to the FDA, generic drug applicants can begin developing copies of new drugs that are protected by patents well in advance of the patent expiring without fearing a patent infringement action being brought. This allows for earlier development and approval of generic drugs. In addition, this provision has been utilized by pioneer drug companies when developing products that may implicate the utilization of a test tool that is protected by a patent of another company.

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48 Public Law 97-414
49 Public Law 98-417
50 See Roche Products v. Bolar Pharmaceutical, 733 F.2d 858 (Fed. Cir. 1984)
II. Ability to Challenge Patents Prior to Expiration

As discussed in further detail below (See Operation of Patent Linkage), under Hatch-Waxman, an ANDA applicant must submit one of four (4) patent certifications/statements for each of the patents listed in the Orange Book for the RLD. For each patent listed in the Orange Book covering the RLD, an ANDA must make one of the following certifications that “in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug [NDA] for which such investigations were conducted or which claims a use for such [NDA] drug for which the [ANDA] applicant is seeking approval”:

- that such patent information has not been filed [by the NDA holder for listing in the Orange Book] (so called, **Paragraph I Certification**),
- that such patent [listed in the Orange Book] has expired [at the time of filing of the ANDA] (so called, **Paragraph II Certification**),
- [ANDA applicant is not seeking approval of its application until] the date on which such patent [listed in the Orange Book] will expire (so called, **Paragraph III Certification**), or
- that such patent [listed in the Orange Book] is invalid or will not be infringed by the manufacture, use, or sale of the new [generic] drug for which the [ANDA] application is submitted (so called, **Paragraph IV Certification**).

### Patent Certifications

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<td><strong>Paragraph I</strong></td>
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<tr>
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<td>• Listed Patent Has Expired</td>
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<tr>
<td><strong>Paragraph IV</strong></td>
<td>• Patent Is Invalid Or Will Not Be Infringed By the Generic Drug For Which Approval Is Being Sought</td>
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The filing of the ANDA with a Paragraph IV Certification is deemed to be constructive infringement and therefore meeting the requirements to bring a lawsuit in court, which becomes important for generic applicants to have certainty prior to commercially launching their generic drug.

III. Declaratory Judgments

In December 2003, Congress passed the Medicare Modernization Act of 2003\(^{51}\) (MMA), which included provisions on so-called declaratory judgments. Specifically, the MMA included a provision allowing an ANDA applicant to bring a declaratory judgment action for invalidity, non-infringement or

\(^{51}\) Public Law 108-173
unenforceability of a Listed Patent if the NDA holder does not sue within statutory forty-five (45) days of receiving Notice of a Paragraph IV Certification. In light of the potential liability for damages for a generic company if it chooses to market without resolution of all Listed Patents, this is a significant provision that provides a generic applicant with an opportunity to seek such an action if the NDA or Patent Holder does not bring suit on any of the relevant patents.

This provision also has applicability in potentially triggering the one hundred eighty (180) day generic drug exclusivity (Generic Drug Exclusivity). In addition, subsequent ANDA filers to trigger the Generic Drug Exclusivity period of the First Applicant and therefore accelerate their own approval have sometimes used this provision. Furthermore, this provision allows an ANDA applicant to obtain patent certainty on other patents that may or may not have been listed in the Orange Book for the RLD and for which the RLD or Patent Holder did not bring a patent infringement suit. In short, this allows a generic applicant to seek patent certainty as it relates to their drug product without having to commercially launch at risk that could result in significant patent damages.

IV. Carve-Out of Method of Use Patents to Accelerate Approval

For any “method of use” patent listed in the Orange Book for a new drug that is subject of a NDA, the generic applicant can include a statement in their ANDA claiming that they are not seeking approval for that method of use in the labeling of their generic drug (so called, Labeling Carve-Out or viii Statement). To the extent that there are multiple indications approved for the NDA, this allows the generic applicant to carve-out from its labeling patent protected method of use(s) in order to accelerate the approval of its ANDA by the FDA. In other words, the generic applicant does not have to wait for all of the method of use patents to expire, challenge all methods of use patents or have their generic drug label contain all of the approved indications of the NDA as long as at least one (1) same approved indication as the RLD is contained in the label of the generic drug and the omission of the other indication(s) does not make the use of the generic drug less safe (e.g., label).

Anti-Trust Implications

A closely watched area has involved the challenge of patents by generic drug applicants and the RLD / Patent Holder entering into a patent settlement that resolves the underlying patent suit, if filed, and provides a date certain market entry for the generic applicant. As noted above, a patent settlement that is entered into between a pioneer and generic drug company that is determined to violate U.S. antitrust laws causes the First Applicant to forfeit their eligibility for Generic Drug Exclusivity. In addition to the impact on Generic Drug Exclusivity, the anti-trust watch-dog, Federal Trade Commission (FTC) has also targeted the area of patent settlements between pioneer and generic drug companies that involve the pioneer drug company giving some type of payment or consideration to the generic drug company to remain off the market until at least after the date of the settlement. The position of the FTC has been that there should be essentially an outright ban on “reverse payments”, also known as payments by the pioneer company to the generic company to delay the latter’s market entry (so-called “pay for delay” settlements). In 2013, the FTC received support for their anti-trust scrutiny of these types of patent settlements with the Supreme Court of the United States holding that pay for delay settlements between pioneer and generic companies are subject to antitrust scrutiny under a rule of reason analysis52. Consequently, according to a recent January 2016 report issued by the FTC53, the number of so-called reverse payment settlements has dropped significantly from forty (40) in Fiscal Year 2012 to twenty-one (21) in Fiscal Year 2014. Notwithstanding this report, an outstanding policy issue remains whether any type of patent settlement facilitates earlier generic entry or delays generic competition.

52 See FTC v. Actavis, Inc., 133 S. Ct. 2223 (2013)
53 See Agreements Filed with the FTC Under the MMA: Overview of Agreements Filed in Fiscal Year 2014: A Report By the Bureau of Competition, Available at https://www.ftc.gov/reports/agreements-filled-federal-trade-commission-under-medicare-prescription-drug-improvement-0)
Appendix II

Other Effective Patent Enforcement Mechanisms

In addition to the patent enforcement mechanisms identified in this report, there are several other markets around the world that have either implemented similar systems or have organic systems that provide effective protection to incentivize innovation while facilitating access to generic drugs. Some of the more prominent market systems are discussed below.

I. European Union

The European Union (EU), in some respects, is a unified region, with laws and regulations common across the EU. In other respects, each country within the region has set up their own unique laws and regulations which industry must abide by. Currently, inventions can be protected in Europe either by national patents, granted by the competent national IP authorities in EU countries or by European patents granted centrally by the European Patent Office (EPO). In addition, patentees may receive supplementary protection certificates (SPCs) providing up to five years extension to their patent term, with an additional six months upon submission of pediatric data. SPCs were created by EU legislation to offset the loss of patent protection for pharmaceutical products that occurs due to the lengthy testing and clinical trials these products require prior to obtaining regulatory marketing approval. As a result of the varying systems, the EU does not have a unified approach to protection of pharmaceutical patents, and in particular does not have a system of patent linkage per se that is similar to the U.S. system. However, in recognition of the importance of creating a consistent and transparent system of pharmaceutical patent protection, the region has adopted a policy of a regulatory data exclusivity period for pharmaceutical products that is greater than the U.S. that prevents the competent authority from approving the generic drug during this time period. As a result, this regulatory data exclusivity period (ten years, with a possibility of an additional year) is considered long enough to incorporate the remaining life of a pharmaceutical patent in most cases. In addition, individual patent holders have other well-established and reasonably efficient legal means of protecting their patents using the court system, including the availability of preliminary injunctions to prevent the approval/marketing of an infringing generic drug.

II. Japan

Generic drugs are a relatively new phenomenon in Japan, with pioneer companies enjoying relative marketing exclusivity long after the relevant patents have expired. However, as with most countries with national health insurance systems, the Japanese government is looking to control health expenditures and has started to encourage the use of generic drugs. As a result, generic substitution is relatively low compared to the United States, but is growing steadily.

Like the European Union, Japan does not have a formal system of patent linkage. However, Japan’s Ministry of Health, Labor and Welfare (MHLW) Pharmaceutical and Medical Device Agency (PMDA) has an administrative process in place by which it does not approve generic products during the life of the patent that covers the active ingredient. This protection does not extend to new indications or dosages. Furthermore, patent holders may apply for patent term extensions when there are substantial periods during which the patent cannot be worked, as in the case of regulatory approvals, etc. In this manner, patent life may be extended up to an additional five years.

In addition, like the EU, Japan has a generous period of protection for new pharmaceutical products, essentially providing a de facto data exclusivity period. This protection comes through the Post-Marketing Surveillance (PMS) system through which MHLW’s PMDA reviews and re-confirms the safety and

54 http://ec.europa.eu/growth/industry/intellectual-property/patents/index_en.htm
efficacy of new medicines over a period of eight (8) years during which applications for generic products may not be submitted. This period is extended to ten (10) years in the case of orphan or pediatric drugs. New indications also enjoy a similar PMS period of four (4) years.

III. Markets Part of Trans-Pacific Partnership Agreement

The landmark agreement known as the Trans-Pacific Partnership Agreement (TPPA) involves a dozen countries at varying levels of economic development and varying levels of sophistication of their individual pharmaceutical sectors. Some countries, such as the United States, Canada, Singapore, Australia and Japan, have vibrant innovative and generic pharmaceutical sectors, while others such as Vietnam have minimal pharmaceutical presence. More to the point, the TPPA has intellectual property (IP) language that attempts to provide a level playing field across the TPPA countries. While highly contested during the negotiations, some of the IP language is necessarily broad and will remain up to the individual countries to settle some of the finer details.

When it comes to pharmaceutical products, both small and large molecules, the protections laid out in the TPPA largely mirror those found in the United States, especially as it relates to patent enforcement mechanisms. For example, the IP chapter, provides for a system that assures sufficient notification to patent holders when a generic applicant seeks marketing approval for a product that may infringe on its patents. This notification is required to be provided prior to the marketing of such a generic pharmaceutical product, thus allowing the patent holder adequate time to seek preliminary injunctions and/or other remedies through the country’s court system. Alternatively, countries may institute a non-judicial, administrative resolution process that achieves the same purpose.
引言

创新在医药行业的作用，正从延长病人寿命向降低总体医疗支出方向转变，这一点毋庸置疑。通过保护知识产权，特别是专利权，能够促进拯救生命的药物的研发。专利对创新药行业在投入昂贵的资源和大量的时间用于研发起到了关键性的激励作用。基于专利权而获得的独占市场的权利有助于回收研发成本以及回收等待药品获准上市所耗费的成本。一般而言，研究表明，创新药在仿制药上市后会有重大的销售损失：仿制药上市三个月内，创新药会损失大约 75% 的销售额，并在仿制药上市 6 个月内，损失近 80% 的销售额。支持新药研发对全球病患而言至关重要。与此同时，仿制药行业同样是医药系统中的重要部分。世界上许多国家都尝试创建一种平衡的制度，既能通过保护知识产权确保能够得到创新药，又能通过保证仿制药的获得来降低医疗成本。在专利实施制度中，刺激医药创新，这一全球性的需求，总是不可避免地与便于获得低价药品捆绑在一起。

有不同的机制能实施高效的专利实施制度，但所有的运行机制有着如下共性：

- 相关专利的确定：采用一种透明的方式来确定相关的有效专利，例如，在公众可访问的中心库中列举覆盖创新药的专利。
- 仿制药申请通知：仿制药企业在正式开始其药品的审批申请时必须及时通知新药申请批件持有人和/或专利权人。例如，要求仿制药申请人早期通知新药申请批件持有人与专利权人，其已提交了仿制药申请并且打算在覆盖参照性新药的专利过期前将仿制药上市。
- 专利纠纷尽早解决：使专利权人能及时启动侵权法律进程并且在仿制药申请被批准或开始上市前解决专利纠纷。这一制度允许专利权人寻求并获得批准的遏制期、预先禁令或其他临时性执行措施以在一合理期间内解决专利纠纷来阻止仿制药的批准或上市。

透明度以及可预测性这一根本性目标为机制运行提供了支持。在商业性上市或批准前，为创新药和仿制药企业提供机会获得专利的确定性至关重要。在美国，“专利链接制度”能够分别为创新药企业实施专利以及仿制药企业尽早批准上市提供可行性。除了美国之外，其他市场如加拿大和韩国，最近也采取了相似的制度。

1984 年，美国国会通过了立法，即为公所众知晓的 Hatch-Waxman 法案，开创了包括一种有效的专利实施制度在内的美国现代社会医药行业。Hatch- Waxman 法案中专利链接条款，概述了仿制药企业通知专利权人其提交了仿制药申请以求在相关专利过期前获准上市的过程，为专利权人提供了机会提起专利侵权诉讼，阻止美国食

品药品监督管理局（FDA）在专利诉讼期间批准仿制药申请。因此，专利链接制度与 Hatch-Waxman 法案中其他市场独占的制度使得美国成为在创新药和获得仿制药方面最强的国家之一。

- 美国药品市场全球最大，2013 年销售额高达 3397 亿美元。\(^{57}\)
- 全球 5,000 种开发的新药中，有 3,400 种新药是美国开发，2005 年来增长了 40%。\(^{58}\)
- 新药申请（NDA）以及简化新药申请（ANDA）批准的数量仍在增加，并且2010年1月1日到2016年1月28日期间，有 661 件\(^{59}\)NDA/BLAs（生物制品许可证申请）\(^{60}\)被 FDA 批准。
- 661 件新药批准中 179 件是新化学实体（NCE）或者新型药物，包括一个在先批准过的 NCE（27.0%）的新对映体。

同时，由于 Hatch Waxman 法案所达到的平衡：

- 美国仿制药的使用，从 1984 年该法案通过前全部处方药中稍多于 18.6%的比例到 2013 年增长至 86%，\(^{61}\)并且预计 2020 年增长至 90%。\(^{62}\)
- 2010 年 1 月至 2016 年 1 月 28 日期间，FDA 批准了 2,765 件 ANDA 申请。\(^{63}\)
- 在美国，仿制药正使用专利链接机制。661 件 NDA 中 157 件正受到专利挑战，寻求专利过期前进入市场。
- 美国仿制药市场占了全球仿制药市场 45%的比重，2013 年价值 435 亿，并

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57 5 Largest Markets for Pharmaceuticals, 访问于 http://www.fool.com/investing/general/2015/05/12/5-largest-markets-for-pharmaceuticals.aspx
59 这一数据以分别申请的数量为基础，因此能够计算同一活性成分各自多样的浓度或剂型。
63 来源：Drugs@FDA found at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

且预测到 2018 年会以两位数（~11%）的年增长率增长。64

本论文考察多个国家采用的有效的专利实施制度和机制，包括美国、加拿大、韩国，尤其着重考察现代社会美国专利链接制度。本论文回顾美国专利链接的历史与明确的实施规定，向法院及时提起专利挑战以及争议解决，并且通过审阅 2010 年 1 月至 2016 年 1 月期间专利链接有效性。另外，本论文审阅了 Hatch Waxman 法案的条款，直接促进了新药以及更好的药品发展的条款；引入旧款药物更便宜的可替代药品；促进更专业的监管机构以及创设一个稳健的奖励创新与生产效率的医药报销制度。

I. 美国专利链接制度的背景

专利链接制度起源于 1984 年《药品价格竞争和专利期恢复法》，又称为 Hatch Waxman 法案65。美国 1906 年起将药品纳入规制，66 然而，直到 1984 年美国国会通过 Hatch Waxman 法案，仿制药简化申请才被纳入进来，刺激竞争并便于获得物美价廉的仿制药。Hatch Waxman 法案一般而言要求 FDA 不批准那些对某些未过期专利覆盖的在先被批准的 NDA 的仿制药申请（即，ANDA）。同时，Hatch Waxman 法案为创新药行业提供了一系列激励来促进美国医药行业创新，包括在潜在侵权的仿制药进入市场前有机会维护他们的专利权。

A. Hatch Waxman 法案立法历史

Hatch-Waxman 法案的启动来自美国总统吉米·卡特 1978 年关于产业创新挑战的国内政策评述。67 委员会建议之一即延长专利期以补偿专利申请人因其产品等待政府审批前所损失的时间。68 这导致了关于潜在立法的争论69，提供这种延长导致仿制药行业积极推动便于获得仿制药的立法。因此，1984 年 9 月 24 日，美国国会通过了 Hatch-Waxman 法案，该法案由参议员 Orrin Hatch（犹他州）以及现已退休的国
Henry Waxman (加利福尼亚州)在国会议员中引导磋商达成。

B. Hatch Waxman法案对创新药与仿制药行业发展的激励

Hatch-Waxman法案提供了一系列对创新药和仿制药的激励，以促进药品创新和便于获得药品。对创新药产业而言，该法案不仅为该产业提供了专利期延长（PTE）以补偿FDA对NDA常规审批期间所损失的时间，而且将覆盖NDA的专利列举在《经治疗等同性评价批准的药品》（俗称“桔皮书”）70，并规定了市场独占和专利链接。同时，对仿制药产业，Hatch-Waxman法案引入了仿制药简化新药申请，限制了FDA所要求的数据的数量，提供了常规的市场独占并激励挑战桔皮书对批准的新药申请（NDA）列举的专利，这些专利被ANDA所参照（“参照药”或RLD）。专利链接制度的运作本质上体现在ANDA批准过程中，概述了对创新药和仿制药申请人的要求和义务。

1. 简化新药申请

Hatch-Waxman法案通过前，所有的药品都被当做“新”药来规制。这要求寻求仿制药批准的公司要么重复进行创新药申请人做过的昂贵的临床研究，要么找到并提交给FDA支持其药品安全性和有效性的文献资料以及其他公开发表的数据。根据Hatch-Waxman法案，ANDA为仿制药提供了简短的、更合理的流程，与各自的RLD相比，需要具备相同的：

- 活性成分；
- 给药途径；
- 剂型；
- 浓度；
- 标签。

如果仿制药符合这些要求，在大多数情况下，支持ANDA所需要的唯一临床数据就是生物等效性研究，证明药品的吸收速率和吸收程度与RLD相比，在允许的范围内。因此，批准仿制药申请的常规审查范围比新药简化了。

在某些情况下，通过向 FDA 提交请愿书，仿制药申请人对于新药的剂型、浓度或者给药途径方面的改变，也能提交 ANDA 而非 NDA。如果 FDA 认为仿制药申请人已提交充分的信息证明对 RLD 预期的改变并不会改变药理或治疗类别，FDA 将批准这一请愿书（适应性请愿书），并允许对改变提交 ANDA 而不用提交 NDA。ANDA 免除了仿制药高昂的临床试验，高昂的临床试验在 Hatch-Waxman 法案通过前抑制了美国仿制药行业的发展。

2. 对新药及仿制药发展的激励

Hatch-Waxman 法案包含了一系列对创新药和仿制药产业的激励，以保持药品创新以及对药品的获得之间的平衡。Hatch-Waxman 法案的实施之后，对其有着众多修正案来处理创新药和仿制药产业的需求。Hatch-Waxman 法案中最相关的条款以及随后的修正案如下并在附录 1 中详细讨论。
II. 美国专利链接制度的运作

在美国，专利链接的运作包含对 FDA、药品申请人（即，NDA 和 ANDA 批件持有人）以及有效监控并实施该制度的司法系统清晰的角色界定。该制度从 NDA 持有人提交申请之时启动，该申请确定其“权利请求覆盖药品或使用方法”的全部专利。71 对于使用方法专利，NDA 持有人必须提交为该专利权利要求所覆盖的每一指示的描述，被称为“使用方法记叙”。根据 Hatch-Waxman 法案，FDA 公开发表与被批准的 NDA 有关的所有专利信息，包括 NDA 持有人提供的使用方法记叙以及市场独占的存在，如桔皮书中新化学实体独占权。

A. 列举的专利

桔皮书中列举的专利以及独占性信息72 是专利链接制度最初且关键的部分。对每一个列举在桔皮书中的专利而言，ANDA 必须做出任一如下申明，“在申请人看来以及其最大了解程度，与此药品有关的每一个专利，当权利要求覆盖新药的每一专利正在进行仿制试验或是该专利权利要求保护新药的使用，而 ANDA 申请人正寻求批准该药品的使用”：

- 该专利信息未被 NDA 持有人提交列入桔皮书（也称为，第 I 段申明）；
- ANDA 申请提交时，桔皮书中列举的专利已到期（也称为，第 II 段申明）；

71 NDA 持有人也能在 NDA 批准之后提交列举在桔皮书中的专利，只要向 FDA 提交的列举在桔皮书中的专利在 USPTO 授予专利权之日起 30 日内提交。

72 请见 Example Orange Book Listing of Patents For An Approved New Drug (Salix/Valeant Pharmaceutical’s Apriso® (Mesalamine), 访问于 https://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=022301 &Product_No=001&table1=OB_Rx
• ANDA 申请人并不寻求在桔皮书列举的专利过期前获批上市，(也称为，第 III 段申明)或者
• 桔皮书中列举的专利是无效的或者所提交的 ANDA 申请的药品的制造、使用或销售不会侵犯相关专利。(也称为，第 IV 段申明)。

专利申明

第 I 段
• 没有列举的专利

第 II 段
• 列举的专利已过期

第 III 段
• 列举的专利将在某一特定之日到期

第 IV 段
• 专利无效或寻求上市的仿制药并不会侵犯其专利

此外，对于任何 NDA 申请中列举在桔皮书中新药“使用方法”专利，仿制药申请人可以声明其并不将该使用方法放在其 ANDA 标签中以寻求申请获准（也称为，标签分割或第 viii 部分声明）。

B. 仿制药申请人的通知要求

如果仿制药申请人对任何列举在桔皮书中的参照药专利提交了第 III 段申明，FDA 直到该专利到期前不能批准该 ANDA。另外，如果 ANDA 包含对参照药的任何列举的专利的第 IV 段申明，这触发了专利链接的潜在申请以及提交包含了第 IV 段申明的 ANDA 的仿制药申请人向 RLD 以及列举的专利的权利人通知其提交了 ANDA 申请。申请和专利链接的时机取决于仿制药申请人是否在其初始 ANDA 中提交了第 IV 段申明，还是之后对其申请进行了修正，让其包含第 IV 段申明（例如，对一列举的专利，将第 III 段申明改变为第 IV 段申明）。
仿制药申请人对其提交的 ANDA 与第 IV 段申明的通知

### 包含第IV段申明的原始ANDA

- 在收到FDA受理了ANDA申请的回执之日起20日内，将专利挑战以及ANDA的秘密信息，包括专利挑战的基础通知NDA以及列举的专利的专利权人。

### 对任何列举的专利修正或补充的ANDA与第IV段申明

- 在修正或补充之日将专利挑战以及ANDA秘密信息，包括专利挑战的基础，通知NDA以及列举的专利的专利权人。

### C. 专利侵权诉讼&仿制药批准的遏制期

收到专利挑战通知之后，如果 RLD 或列举的专利的专利权人在收到ANDA 持有人专利挑战通知之日起45 日内提起专利侵权诉讼，FDA 在收到 RLD/列举的专利的专利权人的专利挑战通知之日起30 个月内（被称为“遏制期”）将不会批准ANDA，除非地区法院判决该专利无效、未被侵权或者不可实施。在这一情形下，FDA 能在法院判决之日或和解协议达成之日或法院介入达成的和解协议做出之日批准ANDA。由于另一方在推进专利诉讼中不合理地拒绝合作，因而遏制期在一方的请求下也能根据州地方法院的裁量延长或缩短。

### 批准的遏制期可得性&实施

#### 向FDA提出的有著第IV段申明的ANDA

- FDA对ANDA完整性进行审查 & 向申请人发送书面确认

#### 通知&提供秘密信息（CA）

- ANDA申请人将带有CA的通知发送给RLD以及专利权利人
- 含有第IV段申明的原始ANDA，收到书面确认之日起20日内
- 修正的ANDA：修正之日

#### 如果法定期限内提起诉讼引发的遏制期

- 30 个月遏制期：对非NCE的新药，45 日内提起诉讼
- 48 个月或 5 年内提起诉讼
- 遏制期从收到通知之日起计算
- 7 年或 5 年内提起诉讼
- 遏制期从RLD批准之日起计算
如果 NDA 或列举的专利的专利权人未在自收到通知之日起 45 天法定期内提起专利侵权诉讼，FDA 将在完成对 ANDA 的审查后立即批准 ANDA。另一方面，如果在遏制期届满前，地区法院判决 ANDA 侵犯了涉案专利，FDA 直到专利过期或有和解协议或有法院介入的和解协议达成前不能批准 ANDA。如果仿制药申请人向联邦巡回上诉法院（联邦巡回法院）73 上诉，FDA 在联邦巡回法院做出 ANDA 不侵犯涉案专利或专利到期前不能批准 ANDA。

尤其是，在美国，自 Hatch-Waxman 法案通过后对专利链接制度的主要改变之一，是通过 2003 年《医疗现代化法案》74（MMA）限制遏制期的数量并保证 FDA 对指南75的实施。MMA 通过前，在 NDA 获批之后，申请人在美国专利商标局（PTO）核准专利后 30 日内任何时间都能向 FDA 提交新专利以列举在桔皮书中。FDA 之后列举在桔皮书中的专利要求所有新 ANDA 以及未决 ANDA 持有人提交该专利的专利证书，因此会触发另一遏制期。根据 MMA，之已提交过第 IV 段申明的未决的 ANDA 持有人并不要求服从另一遏制期，无论其是否服从于之前的遏制期。但是，对 ANDA 持有人有一个例外，在提交其 ANDA 与原专利陈述，包括一个第 IV 段申明到至少一个列举的专利和一个第 III 段申明到另一列举的专利后，会改变其先前提交的第 III 段申明到第 IV 段申明。在后者的情形下，可令 ANDA 服从于另一遏制期。

遏制期的另一细微差别适用于被 FDA 视为包含 NCE 的 NDA。一般而言，直到 NCE 市场独占期（即，5 年）届满前，ANDA 持有人不能提交包含 NCE 的 NDA 的仿制药申请。该规定有一个例外，如果仿制药申请人意图挑战 NCE 药品列举的专利之一，此情况下 ANDA 能在 NCE 独占期届满前一年起（NCE-1，即，NCE 减去一年）提出。如果 NDA 或专利权人在包含 NCE 的 NDA 获批之日起 4 年后的一年内提出专利侵权诉讼，遏制期将延长包含 NCE 的 NDA 获准之日起消逝的这些时间（如果有的话）至 7 年半。

73 请见 Federal Courts Improvement Act of 1982, Public Law 97-164
74 Public Law 108-173
### 美国专利链接制度利益相关者的作用

#### FDA
- 接收和审查NDA&ANDA申请（必要时服从于30或42个月的批准延期期）
- 维持桔皮书中列举的专利
- 对NCE、NCI以及仿制药等授予市场独占权

#### NDA申请人
- 提交NDA申请
- 识别列举的专利
- 接收通知并酌情提起专利侵权诉讼
- 通知FDA诉讼进展

#### ANDA申请人
- 提交附带第IV段声明的ANDA申请
- 对RLD以及专利权人发送专利挑战通知并提供能接触到的秘密信息
- 通知FDA诉讼进展

#### 法院（地区法院及联邦巡回法院）
- 对专利侵权案件以及上诉做出判决
- 若法院发现案件或争议焦点符合确权判决（DJ），如果NDA持有人未在收到第IV段声明通知之日起45日内起诉，则做出列举专利无效、未被侵权或不可实施的确权判决

### III. 美国 2010 年 1 月至 2016 年 1 月 28 日提交的数据

#### 1. NDA 与 ANDA 提交

在美国，提交药品申请，NDA 或 ANDA，是保密的并不会由FDA公开披露。然而，FDA有时会披露年申请提交量的总体数据。例如，在《处方药使用者费用法案》（PDUFA）执行情况报告中，FDA披露了在2010财年（FY），FDA收到103件NDA以及BLA初始申请，2011财年收到101件，2012财年收到130件，2013财年收到138件以及2014财年收到132件，这段时间共计收到604件申请，每年大约有121件申请。

#### NDA/BLA 申请提交量 (2010-2014 财年)

<table>
<thead>
<tr>
<th>年份</th>
<th>2010财年</th>
<th>2011财年</th>
<th>2012财年</th>
<th>2013财年</th>
<th>2014财年</th>
<th>共计</th>
<th>每财年平均</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA收到的NDA&amp;BLA申请提交量</td>
<td>103</td>
<td>101</td>
<td>130</td>
<td>138</td>
<td>132</td>
<td>604</td>
<td>120.8</td>
</tr>
</tbody>
</table>

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76 专利链接制度的实施中，PTO并不起直接作用。

### NCE 申请提交量 (2010 - 2015)

<table>
<thead>
<tr>
<th>年份</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>共计</th>
<th>平均每年</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCE 申请提交量</td>
<td>23</td>
<td>41</td>
<td>41</td>
<td>36</td>
<td>41</td>
<td>40</td>
<td>222</td>
<td>37</td>
</tr>
</tbody>
</table>

至于仿制药申请的提交（即，ANDA），2010 年 1 月至 2015 年 12 月，只能从《仿制药使用者费用法案》（GDUFA）执行评估以及 FDA 活动报告中获得相应数据，并且第一组数据来自 2013 年。根据 GDUFA 以及活动报告中的数据，2013 年，998 件 ANDA 申请提交，2014 年有 1,269 件申请提交，2015 年有 676 件申请提交，三年内共计 2,943 件申请提交，每年大约 981 件申请提交。

### ANDA 申请提交量 (2013 -2015)

<table>
<thead>
<tr>
<th>年份</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>共计</th>
<th>平均</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANDA 申请提交量</td>
<td>998</td>
<td>1,269</td>
<td>676</td>
<td>2,943</td>
<td>981</td>
</tr>
</tbody>
</table>

80 有多种因素影响 ANDA 年申请提交量，包括，新药专利的有效期，根据 GDUFA 交提出新药申请的成本。根据 GDUFA，仿制药趋于速度，正寻求将它们的资源投资到更复杂、需要更多研发时间的药品的生产中。
2. 专利挑战

与 NDA 和 ANDA 申请数据相似，FDA 没有完整、全面地公开 NDA 专利挑战列表。然而，在产业界的压力之下，FDA 已经开始维护现存 NDA 专利挑战的数据。根据 2010 年 1 月 1 日至 2016 年 1 月 28 日的数据显示，ANDA 申请人共提起 364 件专利挑战，涉及该时间段内的 299 个 NDA，其中 157 件针对 NDA 的专利挑战被批准。因此，2010 年 1 月 1 日至 2016 年 1 月 28 日批准的 663 件新药申请中，有大约 23.7%受制于包含第 IV 段申明（即专利挑战）的 ANDA。

3. ANDA 的驳回或迟延

如前所述，2010 年 1 月 1 日至 2016 年 1 月 28 日期间，FDA 批准了约 661 件 NDA/BLA，年平均约 130 件。在 661 件批准的申请中，仿制药企业对其中 157 件 NDA 提交了附带第 IV 段申明的 ANDA。假设 RLD 或专利权人在 45 天法定期内对这 157 件 ANDA 提起专利侵权诉讼，根据遏制期的规定，该等 ANDA 申请在 30 或 42 个月内不能被批准（请见专利链接的运作）。对这附带第 IV 段申明的 157 件 ANDA，有 5 件 ANDA，或者说，有 3.18%收到了 FDA 临时性批准，尽管遏制期届满并且可推定法院并不会延长。此外，根据公开信息显示，15 件或接近 9.55% 的 ANDA 既没有临时性批准，也没有最终获得正式批准。因此，在 157 件附带第 IV 段申明的 ANDA 中，20 件或接近 12.7% 的 ANDA 有资格最终获得正式批准，却很可能因为监管上不批准导致延迟。最重要的是，在这 157 件 ANDA 中，剩余的 38 件或接近 23.7% 的 ANDA 很可能在已经收到正式批准后，却仍然处于未被法院缩短的遏制期内。

<table>
<thead>
<tr>
<th>ANDA Status</th>
<th>504:2010 年 1 月 1 日至 2016 年 1 月 28 日期间批准的未在第 IV 段列表中的 NDA/BLA 数量</th>
</tr>
</thead>
<tbody>
<tr>
<td>5:ANDA 临时性批准的数量</td>
<td>5:ANDA 临时性批准的数量</td>
</tr>
<tr>
<td>15:遏制期届满后既未获得临时性批准又未最终获得批准的 ANDA 数量</td>
<td>15:遏制期届满后既未获得临时性批准又未最终获得批准的 ANDA 数量</td>
</tr>
<tr>
<td>38:最终获得批准的 ANDA 数量</td>
<td>38:最终获得批准的 ANDA 数量</td>
</tr>
<tr>
<td>99:仍处于遏制期的 ANDA 数量</td>
<td>99:仍处于遏制期的 ANDA 数量</td>
</tr>
</tbody>
</table>
4. 专利期

通过审阅 FDA 在 2010 年 1 月 1 日至 2016 年 1 月 28 日期间批准的 661 件包含 NCE 的新药申请列举在桔皮书中的专利信息，在 NDA 被批准之时列举的专利平均有 11.25 年剩余专利期。

5. 专利期延长

FDA 在 2010 年 1 月 1 日至 2016 年 1 月 28 日期间批准的 661 件 NDA/BLA 中，31 件覆盖这些药品申请的专利获得了专利期延长，这代表了略多于 4.5% 的申请 (4.68%)。需注意，这里不包括未决的延长请求，而是包含 1 件一年的临时性延长以及覆盖多于一件申请的 6 件列举的专利。平均专利期延长的长度为 1,140.87 天，或大约延长 3.12 年。专利期延长的范围由 72 天到最长 5 年。

此外，在 2010 年 1 月 1 日至 2016 年 1 月 28 日批准的 NDA 中，有 37 件 NDA 在收到专利期延长批准的同时受到了 FDA 第 IV 段列表上的专利挑战。这些专利期延长的期限从 18 天到最长 5 年，平均 1,238.56 天或 3.39 年。

IV. 关键市场的专利实施制度和机制

世界各国和地区在自己的司法辖区内发展了不同的药品专利保护制度，他们各自的效果反过来塑造了本土医药产业的形成和发展。在部分例子中，医药产业形成于 19 世纪或 19 世纪之前，而另外一些医药公司只是近期才开始在国内制造和/或研发。最后，国内医药产业形成和成功的一个主要原因在于该国的医疗报销制度。

A. 加拿大

加拿大的专利链接制度包含在其《专利药品（批准通知）实施细则》 (“PM (NOC)”)) 中，旨在通过阻止卫生部长 (MoH) 颁布批准通知 (NOC)（即，药品批准）来防止仿制药侵犯专利。加拿大 PM (NOC) 制度与美国 Hatch-Waxman 法案专利链接制度有着众多相似之处，包括：

- 新药提交 (NDS) 的持有人（例如，NDA）必须向 MoH 提交覆盖其新药的相关专利信息
- 专利登记簿（与桔皮书相似）用来维持本国受批准的全部药品
- 在参照专利登记簿中列举的药品，提交之后的或第二件有着相关专利的（例如，仿制药）申请之时，之后的/第二件申请人必须提交对每一项列举的专利的声明，指出：

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82 来源：Source: Drugs@FDA; See Also，www.regulations.gov
83 Patented Medicines Regulations (SOR/93-133) (Last Amended, June 19, 2015)
○ 接受直到专利届满后才会颁发批准通知；或者
○ 做出如下 4 项指控之一（指控通知）：
  ▪ 专利登记簿中专利的提交人虚假地做出其是权利人或得到专利权人同意的声明；
  ▪ 专利已过期；
  ▪ 专利无效；或
  ▪ 仿制药品将不会侵犯该专利。

• 指控通知与仿制药信息（例如，剂型、用途等）以及指控所依据的法律和事实基础一起必须在申请提交之时或之后提供给 NDS 持有人
• NDS 持有人在收到指控通知之日起 45 日内向法院提出诉讼，阻止 MoH 批准仿制药直到专利届满以及协助 MoH 将在法院提出诉讼的事实通知对方
• 因此，MoH 直到 24 个月后方能向仿制药申请人颁发 NOC，在此期间法院对案件做出实质判决（例如侵权或有效性）
• 24 个月的时间期限能被延长或缩短，如果双方同意或者法院发现任一方在诉讼过程中不合理地不配合

此外，与美国联邦贸易委员会（FTC）相似，加拿大也采取了对涉及所谓反向支付的专利和解协议进行严格审查84（请见附录 I 对反垄断的讨论）。

B. 韩国

韩国的医药产业相对比较年轻，主要强调国内产业中仿制药的本土生产和上市。韩国的创新药产业还比较脆弱，只有少数企业对创新药投资进行研发，不管是对本地还是出口市场。最近，韩国政府开始鼓励本国企业开发其药品特别是创新药的出口市场。政府意识到医药报销创新的重要性，并进行了大量改革以使创新方面的投资更有吸引力。值得注意的是，一些改革措施已写入 2012 年《美韩自由贸易协定》。

专利审批链接制度（PALS）是对《韩国药事法》（Korea’s Pharmaceutical Affairs Act）一项相对较新的补充，2012 年初步实施，2015 年 3 月全面实施。就其本身，韩国在专利链接规制方面的实践还是有限。尽管如此，在许多方面，韩国 PALS 仿效了美国的专利链接制度：

• 与美国的制度类似，收到韩国食品药品安全局（MFDS）上市批准的创新药企业必须在 30 日内告知哪些专利与它们的药品有关85。

85 然而，MFDS 会对创新药企业列举的专利额外评估其有效性，也许会在某些标准并未达到时删除这些专利。第三方，例如仿制药企业，也可以有机会提交它们的意见。另外，创新药企业可以对 MFDS 关于哪些专利通过专利链接审批法庭的决定进行上诉。只有 MFDS 批准后这些专利才能列入名单中（类似 FDA 橘皮书）。
当仿制药申请人申请在韩国上市时，仿制药申请人必须对列举在所谓绿名单中的每项专利做出如下6项申明其一：

- 该专利已到期（第1项申明）
- 专利届满前不寻求上市（第2项申明）
- 专利权人以及列举的实体已承认免除仿制药申请人的通知义务（第3项申明）
- 韩国知识产权法庭或法院对列举的专利已判决无效，或者寻求上市的仿制药落在列举的专利范围之外（第4项申明）
- 列举的专利与正寻求上市的仿制药无关（第5项申明）
- 列举的专利无效，或者即使有效但不会被侵犯（第6项申明）

如果申请人做出第6项申明，仿制药申请人必须在申请之日起20天内通知专利权人（专利挑战通知）。专利权人在收到专利挑战通知之日起45天内向MFDS部长提出反对仿制药销售的遏制期请求。

遏制期一旦被授予，其仅在通知之日起9个月内有效，最重要的是，并不会禁止仿制药的批准。相反，它禁止的是仿制药的销售。

同样，与美国相似，韩国的制度激励仿制药企业尽早申请上市批准。先申请的申请人可以得到多达9个月市场独占期，如果它们：

- 最先得到法院的有利判决或专利无效的判决或不侵犯专利的判决；
- 在收到专利挑战通知之日起9个月内获得法院的有利判决。

总之，有众多条款与美国的制度类似，例如通知专利权人以及新药申请持有人，但也有一些关键的不同，例如在遏制期内只是禁止仿制药的销售，并不禁止仿制药本身的批准。

V. 可供中国采用的模式&选择

多年来，中国已成为出口至美国及其他市场的原料药（APIs）的头等供应国。多数原料药被仿制药企业用于在美国、加拿大等发达国家上市的药物制剂(FDFs)。API以及仿制药制剂生产商主导着中国药品市场，并且尽管政府对中国国内企业开发创新药投入了大量资金，只有不成比例的少量中国国内企业开发创新药。如本报告中所指出的，创新药的开发，不仅对资源有要求，还要求具有一个尊重专利的获得和专利实施的创新前的生态系统。若没有制度为创新药企业提供及时的实施其专利的机会，来防止仿制药企业对新药的潜在的侵权，新药研发的投资激励是不存在的。这使得制药行业选择开发更容易、投资回报期更短的仿制药。

根据2015年3月3日的修订，对列举的专利在仿制药最初申请之日起14日内提起专利挑战的仿制药申请也可能有资格获得独占权。
如果中国对制药行业实行专利实施制度，该报告中概述了几款模式能够为中国建立自己的机制提供基础。制度的基础应包括：(i) 创新药企业列举专利；(ii) 覆盖创新药的相关专利到期前，仿制药企业做出早期通知；(iii) 创新药企业对专利有效性以及可实施性寻求司法裁判的机会；(iv) 在创新药企业以及仿制药申请人寻求专利确定性期间，SFDA 一定期间内暂时不批准仿制药申请。

VI. 结论

专利链接制度以及 Hatch-Waxman 法案概述的其他激励对美国创新药和仿制药产业市场的增长起到了根本性的作用。虽然持续增长的新药申请量与之相伴增长的仿制药替代率中可见一斑，但美国制度至关重要的组成部分就是通常被称为专利链接制度的专利实施制度和机制。该专利链接制度必不可少的要素包括清晰明确的创新药与仿制药申请人守则，通过法院系统及时地解决专利挑战，给予对创新药和仿制药企业激励开发新的更好的药品，并且引入更便宜的药品替换旧款药，以及有一行政管理职能的监管者（即 FDA）实施该制度。

因此，Hatch-Waxman 法案专利链接制度配对创新药和仿制药企业的激励和独占权，直接促进了美国制药产业成为世界上价值最高的独大市场。此外，美国医药市场有着高达 80%的仿制药替代率，与此形成对比的是 Hatch-Waxman 法案实施第一年只有 20%的替代率。最重要的是，降低仿制药产业潜在的专利侵权损失对仿制药产业极为有利。为创新药企业提供方法阻止侵权的仿制药上市，使其免于全部药品价值因侵权仿制药上市毁于一旦，创新药企业对专利链接制度受益匪浅。

美国并非是实行保护创新药企业新药价值的专利实施机制唯一的国家。加拿大和韩国同样实行与美国制度有着众多共同属性的平衡创新药企业和仿制药申请人利益的制度。此外，日本和欧盟等市场同样有着对该产业提供类似机会的其他类型的机制（例如，预先禁令）。总体言之，尊重创新的共同目标，专利在创新中的作用，对仿制药申请人提供专利确定性、透明度以及可预测性都在世界众多市场成功实施。
## 共同的专利实施要素

<table>
<thead>
<tr>
<th>国家</th>
<th>加拿大</th>
<th>韩国</th>
<th>美国</th>
</tr>
</thead>
<tbody>
<tr>
<td>创新者列举的专利</td>
<td>专利登记簿</td>
<td>绿名单</td>
<td>枯皮书</td>
</tr>
<tr>
<td>挑战列举的专利的能力</td>
<td>有</td>
<td>有</td>
<td>有</td>
</tr>
<tr>
<td>仿制药申请人通知</td>
<td>指控通知</td>
<td>专利挑战通知申请之日起 20 日内</td>
<td>专利挑战通知申请之日起 20 日内</td>
</tr>
<tr>
<td>遏制期</td>
<td>24 个月</td>
<td>9 个月</td>
<td>30 个月或 7 年半从 NCE 新药获批之日起</td>
</tr>
<tr>
<td>创新药企业提起诉讼的能力 遏制期发挥作用</td>
<td>收到指控通知之日起 45 日内</td>
<td>收到专利挑战之日起 45 日内</td>
<td>收到专利挑战之日起 45 日内</td>
</tr>
</tbody>
</table>
附录 I

新药激励

I. 专利期延长（PTE）

Hatch-Waxman 法案通过后，专利权人和 NDA 申请人有资格申请 PTE 来恢复因为专利所覆盖的新药在 FDA 批准上市前不能上市而使得专利在早期所损失的部分专利期。专利保护期延长的请求必须在收到新药被 FDA 批准上市通知 60 天之内向美国专利商标局（PTO）提出。符合条件的专利最多可获得不超过 5 年的 PTE，且药品通过 FDA 批准后最终专利期不得超过 14 年。一般而言，一种新药只能申请一次专利期延长，如果该药此前未被批准。如果对同一药品有多个专利期延长的申请，默然延长更早过期的专利。此外，如果覆盖多个新药的 1 件专利进入常规性审查，只能有一个专利期延长。

专利的 PTE 计算方式为：新药试验阶段（例如，新药调查阶段）时长的二分之一，加上 FDA 审批新药申请的全部时长。然而，如果新药试验阶段与新药审批阶段的任一阶段发生于专利授予之前，或者专利申请人在临床试验以及评审阶段未尽相应职责，则可适用的延长期需要减去相应时长。同时，PTE 只会由某一药品将更早过期的专利获得。换言之，如果同一药品有两件或多件专利有资格获得 PTE，则将会更早过期的专利被授予延长期。获得延长期的专利会在桔皮书中为多个专利列出来。

87 有资格获得专利期延长的专利，如果其权利要求也覆盖 FDA 批准之外的药品，该专利初始有效期届满后专利过期，无论其是否覆盖其他药品。
**PTE 资格&方法**

### 资格要求

- 专利权利要求保护的是产品、使用方法或制造方法
- 专利未过期
- 专利此前为被延长
- 权利要求保护的药品在上市/使用前服从于FDA审批
- 药品批准是药品首次上市批准
- 每件药品只有1次专利期延长
- 申请人在收到FDA药品批准后60日内向USPTO提出延长请求

### 延长期计算

- 1/2 实验阶段+ 审批阶段
  - **实验阶段**: NDA提交后有效的新药临床研究申请（IND）日
  - **审批阶段**: NDA提交至FDA日起算
- 最多5年延长期
- 不能使得剩余专利期超过14年

1993年，获得的PTE得以扩展，如果申请人有合理理由认为覆盖其药品的专利会在NDA被FDA批准前过期，该PTE可以被中止。初始的专利过期日前6个月到15天，专利人可以请求专利延长期中止。

II. 专利信息的提交&某些ANDA的在先通知

为保证NDA以及专利人（这两者可能并不同一）能够有机会保护他们的发明，Hatch-Waxman法案要求NDA申请人确认并向FDA提交权利要求覆盖该药品或覆盖其使用方法的所有相关专利列表。然而，FDA并不允许某些专利的提交，比如制造方法专利。覆盖NDA的专利信息的提交需要在申请提交（即，NDA）以及常规性申请审查阶段提出。然而，也有情形是，一项NDA批准后，一项新的专利被授予并且该专利由NDA申请人提交至FDA。此外，对于使用方法专利，NDA持有人必须向FDA提交该专利覆盖的每一指示的描述。对这些指示的描述被称为“使用方法记叙”。而且，FDA对所有的专利信息公开在桔皮书中，包括使用方法记叙和/或授予被批准的NDA申请人的专利延长期。FDA为每一获批的NDA列举在桔皮书中的专利信息通常被称为“列举的专利”。

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89 Public Law 103-179, Section 5
特别是，FDA并不独自查证NDA申请人提交的专利信息（例如，使用方法记叙）。稍后会进一步详细论述（请见专利链接制度运作），如果仿制药申请人挑战专利有效性，申明并不侵犯覆盖RLD的任一列举的专利或者该专利不可实施。ANDA持有人必须将其提交ANDA申请以及该ANDA申请的保密信息通知并提供给NDA申请人及专利权人。这有效地在桔皮书上任一列举的专利过期前将仿制药申请人正寻求获得FDA批准的通知事先提供给NDA/RLD及专利权人。收到通知后，如果NDA和/或专利权人在收到通知后45天法定期限内提出专利侵权诉讼，FDA在30个月内不得最终批准ANDA，特定情形下或长或短于30个月。（遏制期）

III. 遏制期

在收到ANDA持有人通知后，ANDA所参照的新药（通常被称为RLD）的NDA或专利权人，能够在收到通知之日起45日法定期内提起专利侵权诉讼，从而触发批准的遏制期，该期间内FDA不能批准仿制药申请（即，ANDA）。如果RLD含有新化学实体（NCE）或新分子实体（NME），生效的遏制期会被延长至从NDA被批准之日起7年半，如果专利挑战在NDA批准之后48个月到5年之内提出。遏制期能提早终结，如果法院做出有利判决，认为有关专利无效、未被侵权或不可实施。在所有情况下，在判决发布前，美国地方法院可以对减少或延长遏制期进行裁量，如果一方不予配合或者故意延误专利诉讼程序。尤其是，只有在提起ANDA申请时列举在桔皮书中的专利能够触发遏制期。因此，1个ANDA申请只允许1次遏制期适用，除非ANDA申请人在申请时最初并没有对RLD列举的专利提出专利挑战但随后将第III段申明变更为第IV段申明。

IV. 新化学实体独占权

如果NDA权利人1984年9月24日（即Hatch-Waxman法案通过）后向FDA提交了含有未曾被批准过的活性成分的药品的审批申请，而且临床研究已经开始（例如，临床试验），FDA将不予受理该参照RLD的ANDA的申请，直到新药批准上市之日5年期限届满。然而，如果ANDA向含有NCE的RLD列举的专利提出专利挑战，ANDA申请能在RLD批准上市之日48个月后提出。如果并无含有NCE的RLD列举的专利，ANDA只有在NCE5年市场独占期过期后提出。

91 除仿制药申请人提交ANDA之外，申请人也可以通过提交所谓第505(b)(2)申请来寻求批准上市，该申请同样会引发与基于Section505(j)/ANDA提交的ANDA相同的专利申明、通知以及遏制期。

92 对于未被桔皮书列举的专利，仿制药企业一般会获得自由实践。同样，也没有什么能排除NDA或专利权人对这些未列举的专利质疑仿制药申请。

93 NDA或专利权人并不受制于必须在45天法定期内提出专利侵权诉讼，只是为获得批准的遏制期，必须在法定期内提起诉讼。

94 在规章的解释中-21CFR§314.08(a)–活性成分一般被定义为“一种活性部分”
为刺激创新，2007 年，美国国会修订 Hatch-Waxman 法案并通过了《食品药品监督管理局修订法案》\(^{95}\) (2007FDAAA)，并被 2012 年《食品药品监督管理局安全与创新法案》\(^{96}\) (2012FDASIA) 重新修订。根据 2007FDAAA 以及重新修订的 2012FDASIA，5 年的 NCE 排他性资格被扩展为包含非外消旋药物，其被包含在先前被 FDA 的另一项应用中被批准的外消旋药物中作为单一对映体的活性成分\(^{97}\)。这有效地促进了该产业继续分离并测试对映体纯度以使得其最终能被开发为药品。例如，法律改变前开发的产品如 Clarinex® (氯雷他定到地氯雷他定) 和 Xyzal® (西替利嗪到盐酸左西替利嗪)有资格获得额外的 5 年独占期。

但是，非外消旋药物 NDA 申请必须满足若干条件才能获得 5 年 NCE 独占期，包括但不限于，1) 审批所需的新的临床医学研究 (NCI) 而非生物等效性研究的完整报告，2) 并非依赖于以前提交的 NCI，并且 3) 使用条件与之前批准的外消旋药物或另一个对映体不是同一治疗种类。

2014 年 10 月 10 日，FDA 以发布产业指南- 新化学实体独占权- 确定特定的固定剂量组合 (FDC) 的药物产品，它能包含 NCE 和一个之前批准的活性组分的 FDC 可能授予 5 年的 NCE 排他性。以市场独占权的方式有效地激励了创新药企业开发可能包含此前批准过的但并不在同一化合物中的活性成分的新药。

对包括适格的非外消旋药物新药以及含有 NCE 的 FDC 的新药而言，如果 ANDA 包含专利挑战，仿制药申请人则在 RLD 批准之日 48 个月之后对其提起。然而，如果 RLD 权利人在 RLD 批准之日 48 个月后的一年内提起专利侵权诉讼，FDA 直到 RLD 批准之日起三年半的期限过后方可批准 ANDA。

V. 新临床研究 (NCI) 独占权

根据 Hatch-Waxman 法案，对 1984 年 9 月 24 日之后 NDA 持有人提起的含有曾在另一申请中被批准的活性成分的药品，以及包含有新药审批关键性的 NCI 报告 (而非其他生物等效性研究) 的药品，FDA 也能授予 3 年市场独占期。相较 NCE 独占权而言，NCI 独占权不排除参考 RLD 而独立提出的仿制药申请，然而，FDA 对于这一受保护的改变的批准不得在 3 年内做出。NCI 独占权最常见的几种用途和

95 Public Law 110-85
96 Public Law 112-144
97 简而言之，对映体是一类立体异构物，它是相互非重叠的全镜相结构。对映体可以是“左旋的”或“右旋的”，其消旋混合物是具有同等量的特定手性分子的左旋和右旋对映体。
适用是新的说明书和剂型的批准（例如，新适应症排他权的 Nexium IV (I-679)\(^9\)，新配方(口腔崩解片)的 Zomig – ZMT \(^{100}\)。 

VI. 儿科用药独占权

1997 年 11 月，鉴于儿科（即 16 周岁以下）用药使用信息的匮乏，美国国会通过了《FDA 现代化医疗法案》（FDAMA），\(^{101}\)引入了儿科用药独占并给予桔皮书列举的 RLD 专利期或原有市场独占期有效期基础上增加 6 个月作为保护期限。起初，只是规定 2002 年 1 月 1 日起试行 5 年，但 2002 年 1 月 4 日，美国国会通过了《最佳儿童用药法》，将儿科条款重新授权发布增加了 5 年试行期限，直到 2012 年其成为《FDA 安全与创新法案》中 FFDCA 永久组成部分。除了 BPCA 中将儿科用药独占权条款作为了永久组成部分之外，FDAISA 也制定了永久性的 2003 年《儿科研效益法案》（PREA2003）,规定了儿科用药评估的诸多要求\(^{102}\)。

VII. 合格传染病产品独占权

根据 FDASIA 第 VII 部分（产生抗生素的诱因），FDA 在批准 NDA 时，也可对指定为 GIDP 药品的 NDA（例如，NCE, NCI, 儿科用药）的某些现有的独占期额外授予 5 年独占期。例如，有资格获得 5 年独占期的含有 NCE 的新药，如果在批准时认定为 QIDP，将会获得额外 5 年共计 10 年的独占期。QIDP 被定义为“治疗严重的或生命威胁性感染的人用抗生素药品”，包括那些由抗生素耐药性病原体、新兴传染病病原体或“合格病原体”引起的感染。合格病原体是指被 FDA 认定并列举的对公共健康造成严重潜在威胁的病原体，例如“耐多药结核”。认定并列举病原体，FDA 考虑多种因素，包括：

- 人体中耐药性生物对公众健康的影响
- 人体中耐药性生物生长速度
- 耐药率的增长

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99 见 Orange Book Patent Information for Nexium IV
https://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=021689 &Product_No=001&table=OB_Rx

100 见 Summary Basis of Approval, 访问于

101 Public Law 105-115

- 在人体中发病率和致死率

此外，FDA 咨询传染病和抗生素耐性方面的专家更新病原体列表。

VIII. 罕用药独占权

Hatch Waxman 法案通过前，美国国会 1983 年通过了《罕用药品法》\(^\text{103}\)，对治疗美国患者总数低于 (i) 20 万人的疾病用药; 或者 (ii) 其药品销量很有可能无法弥补其开发成本的药品以市场独占。该独占权的政策目标是鼓励对目前并无治疗方法的罕见疾病持续的试验以及对罕见疾病治疗现状做出重大改变药品的市场营销。根据这一政策，某些情况下，此前被批准过的药品可能有资格获得该独占权。该市场独占期为 7 年，但与其他独占期而言，其“批准使用条件”限于治疗罕见疾病或状况，而且在此期间不会批准针对同一罕见疾病或状况的随后的药品申请。

仿制药激励

I. Bolar 豁免

作为 Hatch-Waxman 法案中专利期延长的交换，该法案 1984 年 9 月 24 日包括了加入美国《专利法》中的相应条款\(^\text{104}\)，规定对药品专利到期前他人未经专利权人的同意而进口或在美国境内制造、使用、许诺销售或销售专利药品可被合理地视为开发试验，以及在规则制造、使用和销售人用、兽用药品的联邦法下获取 FDA 所要求的数据等信息的行为视为不侵犯专利权。该条款被称为“Bolar 豁免”，它推翻了联邦巡回法院之前的判决\(^\text{105}\)。事实上，为向 FDA 提交数据的目的，仿制药申请人可以对受专利权保护的新药提前进行仿制而不用担心面临专利侵权之诉。这使得仿制药能尽早开发及获准上市。另外，该条款也被创新药企业在开发新药可能会涉及到使用其他公司受专利权保护的测试手段时利用。

II. 专利过期前专利挑战的能力

如之后详述 (请见专利链接运作)，根据 Hatch-Waxman 法案，ANDA 申请人必须提交 RLD 桔皮书中所列举的每一专利的如下 4 项专利申明/声明之一。对于覆盖 RLD 的桔皮书中列举的每一专利，ANDA 申请人必须提交其中一种申明，以申请人根据其观点以及就其最大了解程度，针对权利要求覆盖药品[NDA]的每一个专利，当该权利要求覆盖的新药正在进行仿制试验或是该专利要求保护新药的使用，而 ANDA 申请人正寻求批准该的药品的使用:

- 该专利信息未被 NDA 持有人提交列入桔皮书 (也称为，第 I 段申明)，

\(^{103}\) Public Law 97-414
\(^{104}\) Public Law 98-417
\(^{105}\) 请见 Roche Products v. Bolar Pharmaceutical, 733 F.2d 858 (Fed. Cir. 1984)
ANDA 申请提交时，桔皮书中列举的专利已到期（也称为，第 II 段申明），
ANDA 申请人并不寻求在桔皮书列举的专利过期前获批上市，（也称为，第 III 段申明）或
桔皮书中列举的专利是无效的或者所提交的 ANDA 申请的药品的制造、
使用或销售不会侵犯相关专利。（也称为，第 IV 段申明）

专利申明

第 I 段
• 没有列举的专利

第 II 段
• 列举的专利已过期

第 III 段
• 列举的专利在某一特定之日将过期

第 IV 段
• 专利无效，或者正在寻求批准的仿制药不侵犯其权利

附带第 IV 段申明的 ANDA 的提交被推定为侵权因此符合起诉要求，这对仿制药申请
人将其仿制药上市前确定专利的确定性非常重要。

III. 确权判决

2003 年 12 月，国会通过了 2003 年《医疗现代化法案》106 （MMA），规定了所谓
的确权判决条款。具体而言，MMA 规定了相应条款，在 NDA 持有人未在收到第
IV 段申明之日起 45 天法定期限内提起诉讼时，允许 ANDA 申请人申请对列举的
专利无效、不侵犯专利权或列举的专利不可实施进行确权判决。考虑到如果仿制药企
业选择了对所有列举的专利并没有决议的市场会带来的潜在的赔偿责任，该重要条
款使得仿制药企业在 NDA 或专利权人并没有对相关专利提起诉讼时采取这一行动。

该条款同样还潜在地触发了 180 天仿制药市场独占期（仿制药独占期）。另外，随
后的 ANDA 申请人触发第一申请人的仿制药独占期来加速他们自己的仿制药批准
上市有时也会用到该条款。而且，该条款使得 ANDA 申请人对那些 RLD 可能列举

106 Public Law 108-173
IV. 分割使用方法专利以加速批准

对 NDA 所申请的新药列举在桔皮书中的“使用方法专利”，仿制药申请人可在他们 ANDA 中声明他们对仿制药标签中的使用方法并不要求批准（也称为，标签分割或第 vii 声明）。对于那些一定程度上 NDA 获批的多种适应症，这允许仿制药申请人分割新药标签受保护的使用方法专利以加速 FDA 对其 ANDA 的批准。换言之，仿制药申请人不用非得等到所有的使用方法专利过期，挑战所有的使用方法专利或者让其标签包含所有的 NDA 获准的适应症，只要至少一款与 RLD 相同的获批适应症包含在仿制药的标签上，并且其他的适应症并不会使得仿制药的使用不安全即可（例如，标签）。

反垄断影响

密切关注的领域涉及仿制药申请人提起的专利挑战，以及同 RLD/专利权人可能会达成的解决涉案专利纠纷的专利和解协议，如果有诉讼提起的话，并且，为仿制药市场准入确定了特定的日期。如上所述，创新药企业和仿制药企业达成的专利和解协议被认定违反了美国反垄断法，导致第一申请人丧失仿制药独占权资格。除了对仿制药独占权的影响外，反垄断监管机构，联邦贸易委员会（FTC）也将监管重心放在了创新药企业和仿制药企业达成的专利和解协议方面，一般涉及创新药企业给予仿制药企业某种类型的支付或对价，让其最早在和解协议中规定的日期上市。FTC 的立场在于，“反向支付”需从根本上全面禁止。“反向支付”也被认为是创新药企业支付给仿制药企业推迟其药品上市（所谓“为推迟而支付”协议）。2013 年 FTC 对于这种类型专利和解协议反垄断所采取的严格审查得到了美国最高法院的支持。最高法院也认为，创新药和仿制药企业之间的有偿推迟支付协议应该受到反垄断严格审查。107 因此，FTC 近期发布的 2016 年 1 月的报告 108 显示，所谓的反向支付协议的数量由 2012 财年的 40 件下降到 2014 财年的 21 件。尽管如此，还是存在一个突出的政策问题，专利和解协议究竟是促进仿制药更早进入市场还是推迟仿制药参与竞争。

108 请见 Agreements Filed with the FTC Under the MMA: Overview of Agreements Filed in Fiscal Year 2014: A Report By the Bureau of Competition, 访问于 https://www.ftc.gov/reports/agreements-filed-federal-trade-commission-under-medicare-prescription-drug-improvement-0)
附录 II

其他有效的专利实施机制

除本报告所分析的专利实施机制外，世界上还有其他众多市场要么实施了相似的制度，要么有着有机的制度既对激励创新提供了有效的保护，又便于获得仿制药。一些突出的制度如下所述：

I. 欧盟

欧盟在某些方面是一个统一的地区，整个欧盟拥有共同的法律法规。但另一方面，该地区的各个国家都建立独特的行业法律法规。目前，发明在欧洲既可以由国家知识产权主管部门授予国内专利保护，也可以由欧洲专利局（EPO）集中授权的欧洲专利保护。此外，如果额外提交六个月的儿科数据，专利权人可以获得专利多达 5 年的补充保护许可（SPC）。由于药物产品取得监管机构的上市许可前需要长期的测试和临床试验，使得专利保护出现缺失，欧盟通过立法创造了 SPC 来补偿这种缺失。但由于各国制度差异，欧盟没有统一的保护药品专利的途径，更加没有和美国专利制度类似的专利链接制度。然而，认识到来创建统一、透明的药品专利保护制度的重要性，欧盟制定了药品监管数据独占期政策。该政策优于美国制度，阻止了该时间段内仿制药批准的竞争性授权。因此，该监管数据独占期（10 年，可能延长）已经足够涵盖大多数情况下药物专利剩余的期限。此外，个别专利权人还有其他完善、合理有效的，通过司法制度保护专利的法律途径，包括预先禁令阻止侵权仿制药批准/上市。

II. 日本

在日本，仿制药还是一种相对较新的现象，创新药企业在相关专利期满后很长一段时间内仍享有相对市场独占权。然而，随着大多数国家建立了国家医疗保险系统，日本政府正试图控制医疗经费并且已经开始鼓励使用仿制药。因此，相对美国，仿制药的替代性较低，但在稳步增长中。

与欧盟类似，日本没有正式的专利链接制度。但是，日本的卫生、劳动和福利部（MHLW）药品医疗机器综合机构（PMDA）通过相关行政程序，不允许在活性成分相关的专利有效期内批准仿制药。该保护不延及新适用症或使用剂量。

另外，专利权人可以申请专利期延长，如果有大量期间专利并不能起作用时，例如在常规审批过程中等。该情况下，专利期可额外延长至多达 5 年。

此外，与欧盟类似，日本为新药品提供了很长的保护期，尤其是提供了实际上的数

据独占期间。这种保护通过上市后监管（PMS）制度实现。MHLW 的 PMDA 通过 PMS 制度审查并重新确定不接受仿制药申请的这 8 年内的新药的安全性和有效性。如罕用药或儿科用药，该期间可以被延长至 10 年。新适应症也享有 4 年的类 PMS 期间。

III. 跨太平洋伙伴关系协议

跨太平洋伙伴关系协议（TPPA）是里程碑式的协定。它涉及不同经济发展程度和不同复杂程度制药行业的 12 个国家。一些国家，如美国、加拿大、新加坡、澳大利亚和日本，有蓬勃创新药和仿制药产业，而其他国家，如越南，只有极少的制药业务。更确切地说，TPPA 用知识产权（IP）的语言，试图在 TPPA 国家间建立一个公平竞争的环境。尽管谈判中激烈争辩，但某些 IP 语言一定是广为必要的，并且将为各个国家解决一些精细的问题。

关于药品，无论大小分子，TPPA 的保护很大程度上反映美国制度，特别是专利实施机制。例如，IP 章中规定了当仿制药申请人寻求药品上市时，需要向专利权人提供充分的通知，该药品可能会侵犯其专利。该通知需在仿制药上市之前提供，使得专利权人有充分的时间寻求预先禁令和/或其他法院系统的救济措施。还有另一选择，成员国可建立一能达到同样目的的非司法的行政解决途径。