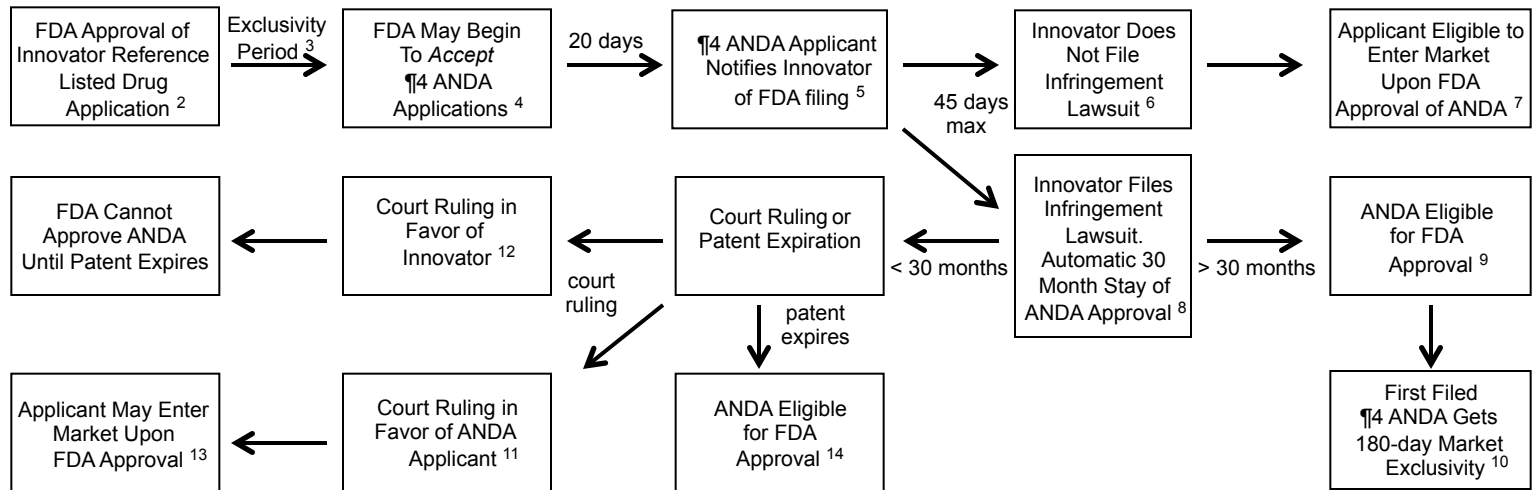


The Hatch-Waxman Act of 1984 ¹:

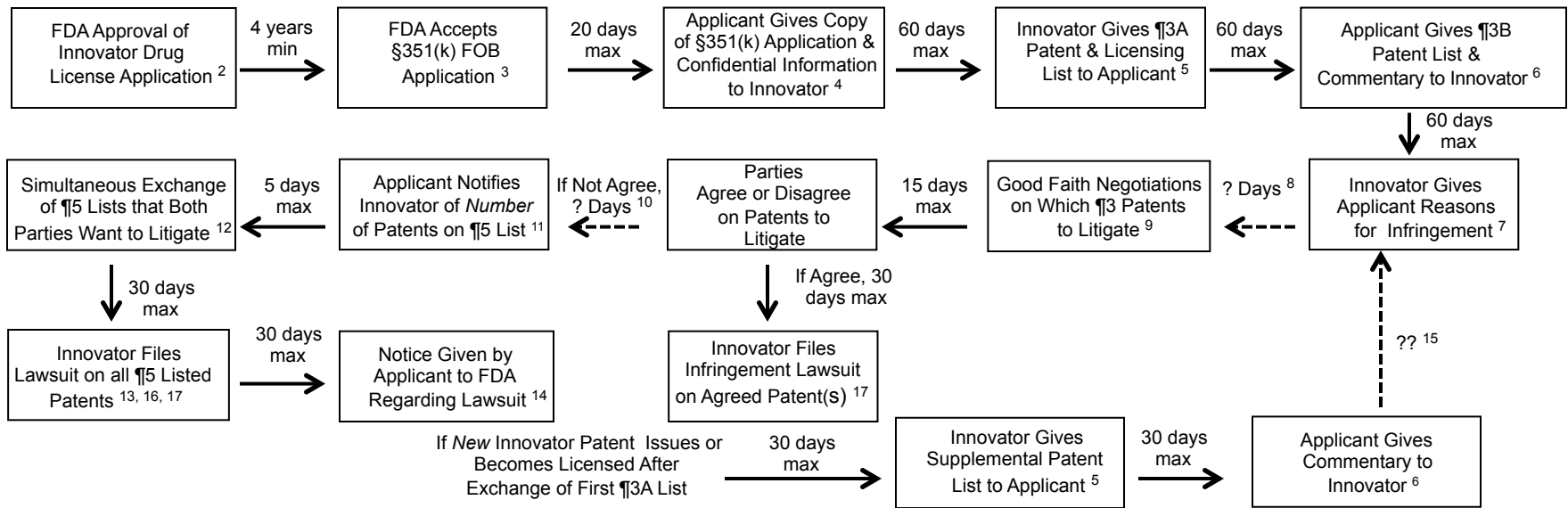
Pre-Litigation Procedure for Market Entry of Generic Small Molecule Drugs



1. Amends the Federal Food, Drug and Cosmetic Act (FDCA) to facilitate Food and Drug Administration (FDA) approval of generic versions of small molecule drugs. Under the Act, generic drug applicants can rely on clinical data from the brand-name reference listed drug (RLD) to show safety and efficacy when submitting an Abbreviated New Drug Application (i.e., ANDA or §505(j)). Applicant need only demonstrate bioequivalence to RLD. See Ch. 5 of the FDCA (§505). See also Ch. 9 of 21 U.S.C. (§§301-399) and Ch. 1 of 21 C.F.R. (§§1-1299).
2. Innovator must list in the Orange Book the patent number(s) of any patent to which a claim of patent infringement could reasonably be made for patents claiming the chemical entity (i.e., RLD), formulation or method of using the drug, along with patent expiration dates, branded drug name, and exclusivity dates. Patents having only “methods of making” claims are not subject to ANDA litigation.
3. New Chemical/Molecular Entity (NCE/NME) status affords 5 years of exclusivity against FDA *acceptance* of subsequent 505(b)(2) applications or ¶1, ¶2, or ¶3 certified ANDAs (See footnote 4 for brief description of ANDA types). FDA may begin to *accept* ¶4 certified applications 4 years after RLD marketing approval. New Clinical Study (NCS) status affords 3 years of exclusivity against *approval* of subsequent 505(b)(2) or ANDA applications. Orphan Drug Exclusivity (ODE) status affords 7 years of exclusivity against *approval* of 505(b)(1), 505(b)(2) or 505(j) applications directed to the same drug (including combination products and different salt forms) *and* the same indication. Pediatric Exclusivity (PED) status affords 6 months of exclusivity beyond any marketing or patent exclusivity against subsequent 505(b)(2) or 505(j) applications. Pediatric studies do not need to be successful to gain PED status. See *generally* 21 U.S.C. §355 a-c.
4. FDA has 60 days to notify applicant that their ANDA is either *accepted* as “substantially complete” or otherwise rejected. Approval or disapproval of ANDA generally occurs within 180 days. Note: A ¶4 ANDA certification seeks to gain market entry *prior* to patent expiration. A ¶1 ANDA certifies that RLD patent information has not been listed in the Orange Book. A ¶2 ANDA certifies that the RLD patent(s) has expired. A ¶3 ANDA certifies that applicant is seeking FDA approval after expiration of RLD patent(s). Alternatively, generic applicant may submit a “Paragraph viii” (i.e., “carve-out”) statement for an unclaimed method of use. The first ANDA applicant(s) to submit a “substantially complete” ¶4 certified ANDA is/are eligible for 180 days of market exclusivity. Submission of an ANDA is an act of patent infringement. See 35 U.S.C. §271(e)(2)(A) and (B).
5. Applicant also must submit statement of factual and legal basis of opinion that patent(s) is/are invalid or will not be infringed.
6. Failure of Innovator to file suit (e.g., “pay-for-delay”) generally precludes subsequent ¶4 ANDA applicants from gaining 180-day market exclusivity.
7. Innovator may sue after 45 days, but 30 month stay is lost and the first “substantially complete” ¶4 ANDA applicant is eligible for 180 days market exclusivity. FDA may only approve subsequent ¶4 ANDA applications once 180 day exclusive marketing period has expired or been forfeited. Applicant may file declaratory judgment (DJ) action if ANDA has ¶4 certification and NDA holder has not sued within 45 days. The NDA holder cannot file a DJ action, except as normally available after generic drug market entry. Failure to market drug, gain tentative approval, withdrawal of application, amendment to ¶4 certification, expiration of all patents or anticompetitive agreements may result in forfeiture of 180 day market exclusivity. See FD&C Act § 505(j)(5)(D).
8. Filing of lawsuit stays FDA approval of the ANDA until the earlier of: (1) the date the patent(s) expire, (2) a final court determination of non-infringement and/or patent invalidity or (3) expiration of the 30 month stay measured from the Innovator’s receipt of notice of the ¶4 certified ANDA. Patent holders are entitled to only one 30 month stay for each ANDA filer (pre-MMA 2003, multiple 30 month stays were possible). Applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information.
9. Applicant must remain diligent during litigation and meet all regulatory requirements to *receive* approval. Applicant who cannot gain tentative ANDA approval within 30 months *may* forfeit the exclusivity period unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed. A generic applicant having an approved ANDA may go to market “at risk” after 30 months if litigation is still in progress.
10. 180-day exclusivity period begins upon the earlier of (a) first commercial marketing of generic drug or (b) the date of a court decision declaring the patent invalid and/or not infringed. Subsequent ANDA applicants (i) may only be approved after first ¶4 ANDA 180-day exclusivity period has been exhausted and (ii) are not eligible for 180-day exclusivity. Subject to FTC scrutiny, RLD sponsor may establish “pay-for-delay” agreement with first ¶4 ANDA filer to block subsequent ¶4 ANDA filers from entering the market.
11. Patent is: (a) invalid, (b) non-infringed and/or (c) unenforceable. Court decision triggers 180-day marketing exclusivity period.
12. Innovator must demonstrate that patent(s) is valid *and* infringed.
13. Court decision triggers 180-day exclusivity period. Applicant who cannot gain tentative ANDA approval *may* forfeit some or all of their exclusivity period (See footnote 9 above). Subsequent FDA approved ¶4 ANDA applicants are not eligible for 180-day exclusivity.
14. 180-day exclusivity does not extend beyond patent expiration date(s). One or more FDA approved ¶4 ANDA applicants can now enter the market.

The Patient Protection and Affordable Care Act of 2010 1:

Pre-Litigation Procedure for Market Entry of Follow-On Biologic Products

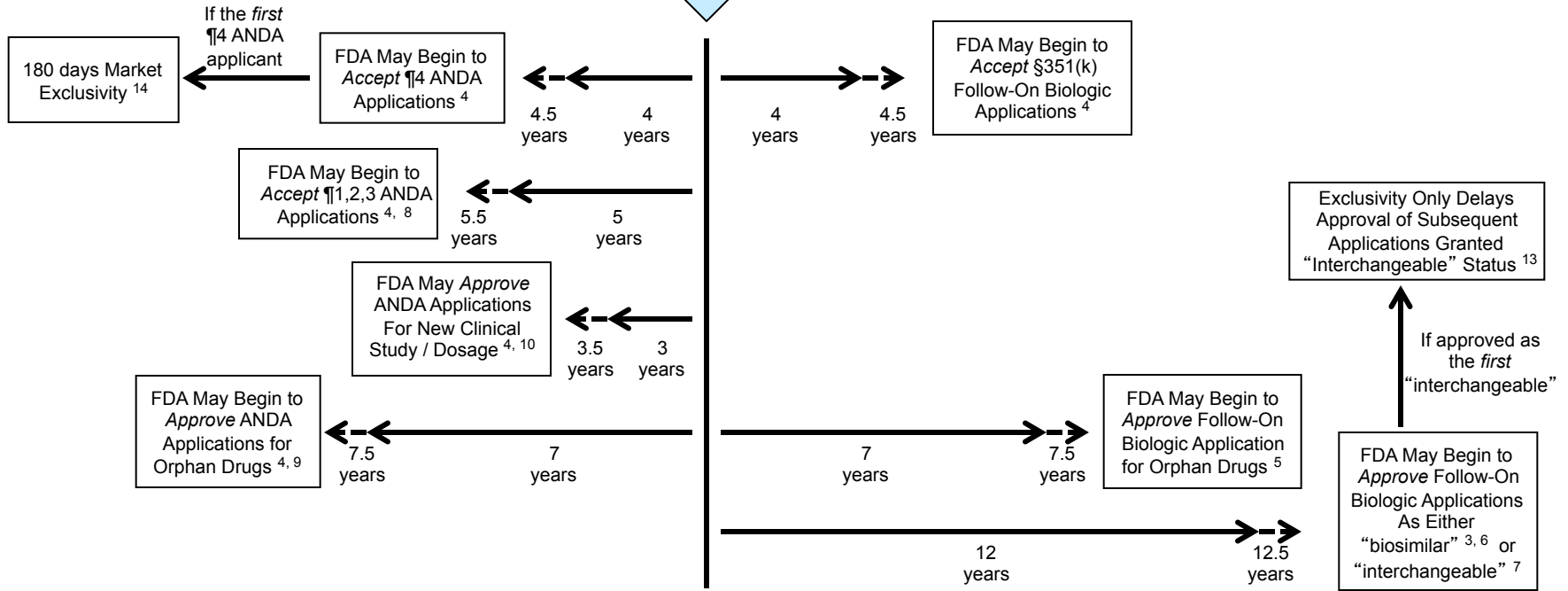


1. The PPACA amends the Public Health Services Act (PHSA) codified under 42 U.S.C. §262. The complex patent pre-litigation procedure is described in detail in §351(l) of the PPACA. The legal and scientific requirements for gaining biosimilar and/or interchangeable status, including market exclusivity periods, are detailed in §351(k) of the PPACA. *This general overview is subject to periodic update to comply with changes in the law.*
2. Either a Biologic License Application (BLA) or a New Drug Application (NDA). Note: there is a 10-year phase-out of NDA applications for biologically defined products. Effective March 23, 2010, except as provided otherwise, an application for a biological product shall be submitted under §351 of the Public Health Service Act (42 U.S.C. §262). See PPACA §7002(e) "Products Previously Approved Under Section 505".
3. The PPACA modifies 35 U.S.C. §271(e)(2) to make the filing of a §351(k) follow-on biologic (FOB) application an act of infringement. There is no automatic stay of litigation - applicant may enter market "at risk" after expiration of any FDA imposed market exclusivity period.
4. Confidential Information (CI) may include proprietary manufacturing methods that are often afforded trade secret legal protection. Referred to as "¶2 Disclosure Requirements." Such information is restricted to unlimited number of outside counsel, one in-house counsel and any single representative of patent owner. Recipients of such information may only be used to evaluate infringement and may not be involved in prosecution of related patents. If litigation ensues, CI remains confidential until a protective order is entered, otherwise, Innovator must return or destroy CI. BLA holder may bring DJ action on any patent if applicant fails to provide FOB information. The DJ action seems to be limited to product and method of use patents and may exclude process and manufacturing patents.
5. Identifies patent(s) for which Innovator believes a claim of infringement could reasonably be asserted (includes methods of manufacture patents and exclusively licensed patents). Innovator's failure to timely list relevant patent(s) may preclude future Declaratory Judgment action on that patent. Innovator also identifies any patent(s) it is willing to license to Applicant. Collectively referred to as "¶3A patents." Newly issued/ licensed patents may be added by day 30.
6. Identifies patent(s), if any, for which Applicant believes a claim of infringement could reasonably be asserted. Referred to as "¶3B patents." If Applicant chooses not to identify any patent(s), Innovator is limited to one patent listing. Commentary may include (a) patent challenges (e.g., invalidity, unenforceability or non-infringement), (b) notice of intent not to market until patent expiration, and (c) response to offer of patent(s) for licensing. BLA holder may bring DJ action if FOB applicant fails to provide commentary.
7. Includes response(s) to patent challenges for all ¶3B patents not originally listed in ¶3A patent list. Note: as ¶3B patents may include some or all ¶3A patents, the response may need to address all ¶3 listed patents.
8. There is no defined time to begin "good faith" negotiations. Presumably, it is a reasonable time.
9. It is uncertain whether either party can initiate negotiations on any ¶3 listed patent(s).
10. There is no defined time period for Applicant to notify Innovator of number of "¶5 patents" patents it believes should be litigated.
11. Not the *identity* of the ¶5 patents. Failure of Applicant to do so in a timely manner may allow Innovator to initiate lawsuit on its own of listed patents of its own choosing.
12. Innovator ¶5 patent list cannot exceed the *number* of patents on Applicant ¶5 list. If Applicant lists no ¶5 patents, Innovator may list only one previously ¶3 listed patent.
13. Innovator must file good-faith lawsuit on all patents listed in both Applicant's and Innovator's ¶5 lists or risk losing relief. Preliminary Injunction (PI) available to Innovator for ¶3 patents that did not mature into ¶5 patents (i.e., "Excluded ¶3 Patents"). While Innovator likely cannot sue on a patent not originally included in the ¶3A list, the Act does not necessarily prohibit filing suit on any ¶3 listed patent.
14. Applicant must additionally give notice to Innovator at least 180 days before market entry of Follow-On Biologic (it is unclear if notice can be given prior to receiving FDA approval). After receiving notification and before commercial marketing, Innovator may file Preliminary Injunction (PI) only on Excluded ¶3 patents. If Applicant complies with all ¶2 Disclosure Requirements, neither Party can bring Declaratory Judgment (DJ) action on any Excluded ¶3 Patent until after the 180 day notice was given. DJ actions may be filed only if the "all the circumstances" analysis is satisfied. If Applicant fails to comply with ¶2 Disclosure Requirements, only Innovator may file DJ on any patent claiming the biological product or use of the product. If Applicant fails to comply with certain post-¶2 requirements, only Innovator may bring DJ action on any ¶3A patent or newly listed or licensed patent.
15. Presumably, the entry of newly issued patents will follow a similar pre-litigation route. For purposes of obtaining a PI, such new patents are treated the same as Excluded ¶3 Patents.
16. Innovator may bring action for Declaratory Judgment for any ¶3A patent or Supplemental Patent if Applicant fails to; (a) exchange patent lists, (b) provide patent commentary, (c) exchange of 351(k) application with manufacturing methods, (d) provide Notice of commercial marketing or (e) notify FDA of pending lawsuit.
17. Failure to bring suit results in exclusive remedy of reasonable royalties.

The Hatch-Waxman Act of 1984¹:
Exclusivity Periods¹¹

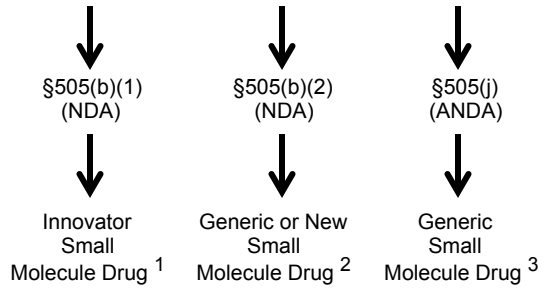
FDA Approval of Small Molecule New Drug Application (e.g., NDA) or Large Molecule Biologics License Application (e.g., BLA)^{3, 6}

The Patient Protection and Affordable Care Act of 2010²:
Exclusivity Periods¹²

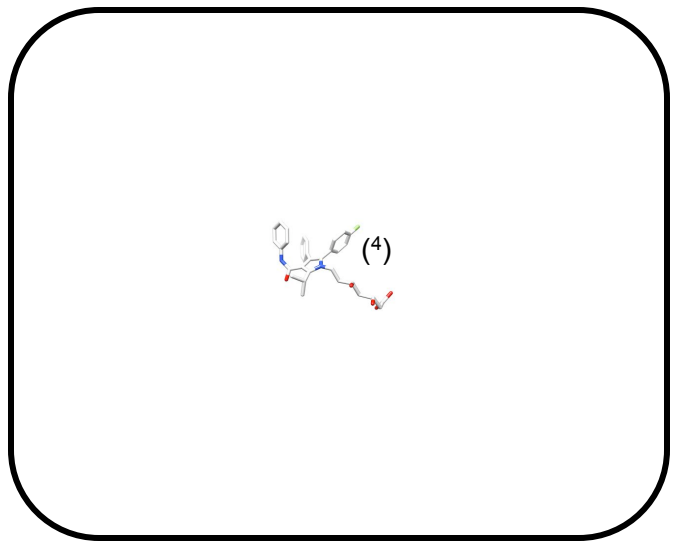
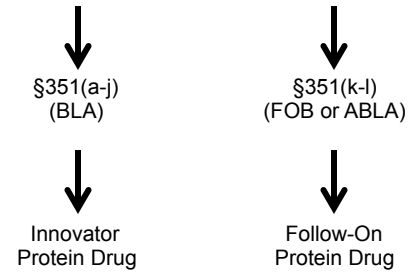


- Amends the Federal Food, Drug and Cosmetic Act (FDCA, 21 U.S.C. §301 *et seq.*). With notable historical exceptions, regulates “small molecule” drugs manufactured by traditional chemical synthesis. *This general overview is subject to periodic update to comply with changes in the law.*
- Amends the Public Health Services Act (PHSA, 42 U.S.C. §262). Regulates “large molecule” protein base drugs derived from living matter or made in living cells using recombinant DNA biotechnology.
- Under the PPACA, there is a 10-year phase-out of NDA applications for biologic drugs already approved under the FDCA. Effective March 23, 2010, except as provided otherwise, an application for a biological product shall be submitted under §351 of the Public Health Service Act (42 U.S.C. §262). See PPACA §7002(e) “Products Previously Approved Under Section 505.” The following are not eligible for a 12-year exclusivity period: (a) supplemental BLA(s), (b) subsequent BLA(s) filed by Innovator for non-structural change(s) resulting in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength, and (c) subsequent BLA(s) filed by Innovator for structural change(s) that do not result in a change in safety, purity or potency.
- PED applies equally to both FDCA and PHSA regulated drugs affording 6 months of exclusivity beyond any marketing and/or patent exclusivity against subsequent 505(b)(2) or 505(j) “ANDA” applications containing same active drug moiety. See 42 U.S.C. §262(m). PED exclusivity may be granted upon FDA acceptance of pediatric study reports. Pediatric studies are requested by the Secretary of the FDA and need not demonstrate pediatric applicability to gain PED status.
- Orphan Drug Exclusivity (ODE) designation and approval is indication specific. Follow-on biologic (FOB) applications for Orphan Drugs may not be approved for the same orphan disease until the later of (a) expiration of the reference drug 7-year ODE period or (b) the 12-year exclusivity period. See 42 U.S.C. §262(l).
- An application for a *structural change* to a previously approved biologic that results in a change in safety, purity or potency *is* eligible for its own 12-year exclusivity period.
- Market exclusivity for follow-on biologics applies only to the *first* biologic approved by FDA as “interchangeable.” Subsequently approved “interchangeable” follow-on biologics are not afforded any market exclusivity.
- New Chemical/Molecular Entity (NCE/NME) status for Innovator drug affords (i) 5 years of exclusivity against FDA *acceptance* of subsequent 505(b)(2) applications or §1, 2, or 3 certified 505(j) applications and (ii) 4 years exclusivity against *acceptance* of §4 505(j) applications. Exclusivity does not apply to another full competitor NDA or BLA if the sponsor has performed all necessary clinical studies.
- Orphan Drug (ODE) status affords 7 years of exclusivity against *approval* of subsequent 505(b)(1), 505(b)(2), or 505(j) applications directed to the same drug (including combination products and different salt forms) for the same disease.
- New Clinical Study (NCS) status affords 3 years of exclusivity against *approval* of subsequent 505(b)(2) or 505(j) applications for that particular indication.
- See 21 U.S.C. §355(j).
- See 42 U.S.C. §262(k).
- The earlier of (a) 1 year after first commercial marketing, (b) 18 months after final court decision, (c) 42 months after approval of first interchangeable if lawsuit still pending or (d) 18 months after approval of first interchangeable if no lawsuit filed. “Final court decision” refers to a court from which no appeal can be taken (i.e., CAFC). Approval of a follow-on biologic with “biosimilar” status affords no exclusivity.
- If multiple 505(j) sponsors file on the same day, 180-day exclusivity is shared. 180-day exclusivity period begins the earlier of (a) commercial marketing or (b) a court decision finding patent invalid, not infringed or unenforceable. 505(j) approval alone does not trigger 180-day period.

FD&C Act (21 U.S.C. §§301-399)

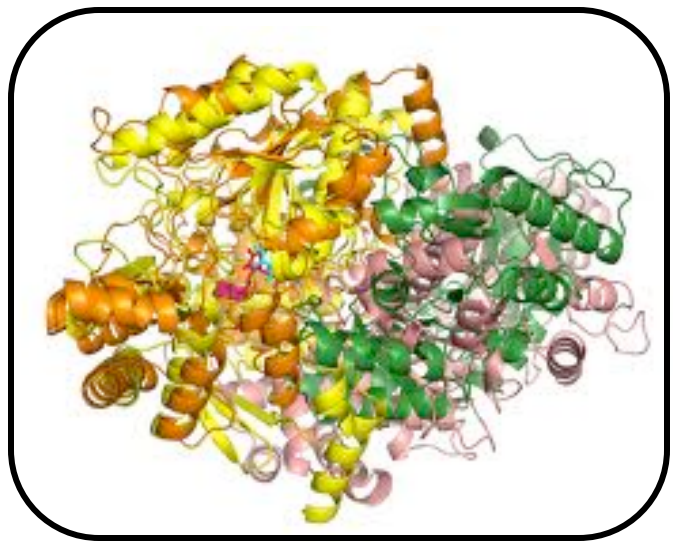


PHS Act (42 U.S.C. §262)



Molecular Weight ~ 1X

Small Size, Fixed Chemical Structure, Easy to Copy, Easy to Characterize

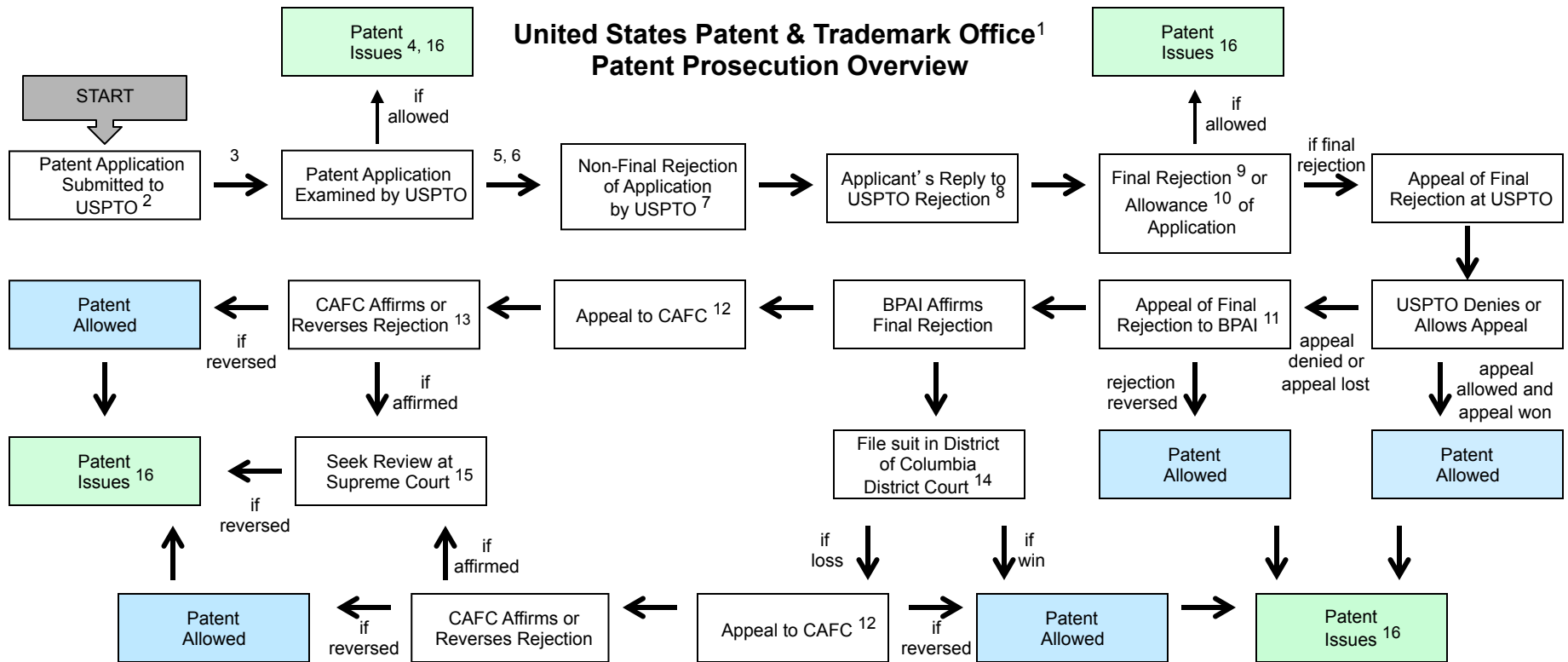


Molecular Weight ~ 1,000 X

Large Size, Variable Chemical Structure, Difficult to Copy, Difficult to Characterize

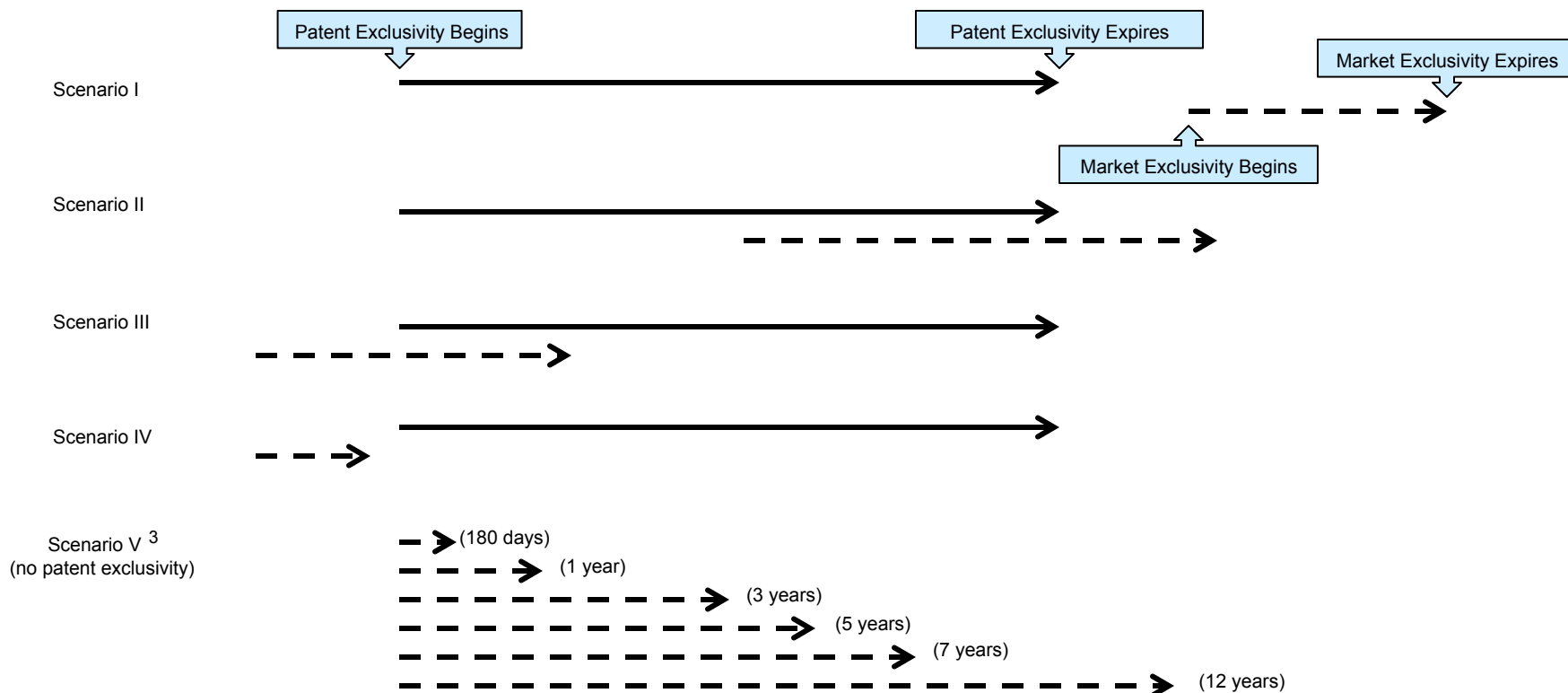
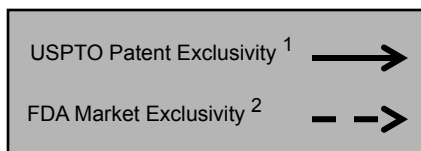
1. Non-abbreviated pathway required for all New Chemical/Molecular Entities (NCE/NME). Relies on costly clinical trial safety and efficacy studies performed by applicant.
 2. Partially-abbreviated pathway relying in part on clinical trial safety and efficacy studies performed by another. Useful for new dosage forms, strengths, dosing regimens and new indications. New clinical trials are not always necessary. Notice to the branded product drug company and patent certification (i.e., ¶1,2,3 or 4) is required.
 3. Fully-abbreviated generic pathway as a result of the Hatch-Waxman Act of 1984. Applicants may begin preclinical or clinical trials prior to patent(s) expiration. Relies on clinical trial safety and efficacy studies not performed by applicant. State substitution laws typically allow for retail pharmacy substitution of an ANDA generic product for the branded reference drug without physician involvement.
 4. Size of small molecule drug is substantially enlarged for clarity. Actual relative size is significantly smaller.

United States Patent & Trademark Office¹ Patent Prosecution Overview



1. Commonly referred to as the USPTO. Located in Alexandria, Virginia adjacent to the U.S. District Court Eastern District of Virginia. This general overview is subject to periodic update to comply with changes in the law.
2. Application may be (a) "Provisional", (b) "Non-Provisional" (includes Divisional, Continuation, or Continuation-in-Part applications) or (c) U.S. entry of a foreign or Patent Cooperation Treaty (PCT) patent application. See Ch. 500 and 600 of the Manual of Patent Examining Procedure (MPEP). For PCT information, See MPEP Ch. 1800. For design or plant patents, See Ch. 1500 and 1600, respectively.
3. USPTO is required to substantively respond to Non-Provisional within 4 months of submission of complete application. Provisional Applications are never substantively examined, but are pending for 12 months. Provisional Applications automatically expire after 12 months. Delays in USPTO or applicant responses may alter term of issued patent. See MPEP Ch. 2700.
4. It is highly unusual that patent application is allowed without being rejected at least once by USPTO. Upon Issuance, a patent is legally enforceable. The *Official Gazette of the United States Patent and Trademark Office for Patents* (OG) is issued every Tuesday and summarizes that week's patented inventions.
5. Applicant may submit preliminary amendments to application to place it in a better condition for allowance.
6. A Restriction Requirement is often issued by the USPTO prior to Non-Final Rejection forcing applicant to (a) elect among "independent and distinct" patentable subject matter for prosecution and/or (b) file Divisional patent application(s). See MPEP Ch. 800.
7. This is often the first substantive legal review of the application. Rejection(s) may include §§ 101, 102, 103 and/or 112 rejections in addition to Restriction Requirements. See MPEP Ch. 700, 800 and 2100.
8. Applicant's reply is typically due in 3 months and extendable up to 6 months. Reply may include argument and/or permissible amendments to application specification and claims. Delays in USPTO or applicant responses may alter enforceable term of issued patent. See MPEP Ch. 2700.
9. Applicants of Finally Rejected patent applications may (a) attempt to enter "after final" amendment to place application in better condition for Allowance, (b) seek an Appeal, (c) seek a Request for Continued Examination (RCE), (d) seek a Continuing Application (CON) or (e) be Abandoned by applicant. Strategic business and legal considerations must be considered in selecting type of reply.
10. Allowance is often a result of applicant successfully arguing or complying with USPTO suggested amendments including narrowing claim scope and satisfying §101, §102, §103 and/or §112 patentability issues.
11. Board of Patent Appeals and Interferences (under USPTO jurisdiction, See MPEP Ch. 1200).
12. Court of Appeals for the Federal Circuit (CAFC).
13. The CAFC is composed of twelve active judges. Typically, appeals from a District Court are heard by a 3 member panel of CAFC judges.
14. Applicant has the option of seeking Appeal at the District of Columbia District Court in lieu of the CAFC.
15. Review is rarely granted by the Supreme Court of the United States (SCOTUS).
16. Upon Issuance, the patent is legally enforceable. See Ch. 1300 MPEP. To maintain enforceability, applicant must pay maintenance fees at 3.5, 7.5 and 11.5 years (maintenance fees are not applicable to design and plant patents). See MPEP Ch. 2500. The enforceable patent term may be positively extended (i.e., PTE) and/or adjusted (i.e., PTA). See MPEP Ch. 2700.

USPTO Patent Exclusivity and FDA Market Exclusivity Possible Scenarios



1. For patent applications filed on or after June 8, 1995, the enforceable term of a patent ends 20 years from U.S. application's filing date. For patent applications filed before June 8, 1995, the enforceable term of a patent ends 17 years from the patent's issue date, regardless of length of patent prosecution. If a patent application was pending or a patent was in force on June 8, 1995, the enforceable term is 17 years from issue or 20 years from application filing in the U.S. – whichever is greater. For applications filed after May 29, 2000, the enforceable term may be extended by Patent Term Adjustment (PTA, See 35 U.S.C. §154) due to delays caused by USPTO during patent prosecution. Patent terms may also be extended via Patent Term Extension (PTE, See 35 U.S.C. §156) due to regulatory delays during FDA drug approval. PTE is *calculated* by FDA (as ½ the period of clinical trials + entire period of FDA review and approval with a 5 year maximum PTE period). PTE is *applied* to the patent term by USPTO. PTE may be added onto PTA, but total extension cannot extend patent term beyond 14 years from date of FDA drug application approval.

2. See 21 U.S.C. §355 and 42 U.S.C. §262. May include one or more of the following: (a) 180 day exclusivity (e.g., for first 14 ANDA applicant), (b) 6 month Pediatric Exclusivity (PED), (c) 1 year exclusivity (e.g., for first approved "interchangeable" follow-on biologic), (d) 3 to 5 year exclusivity (e.g., for 505(b)(2) applications), (e) 5 years new chemical/molecular entity (NCE/NME) exclusivity pursuant to approval of a 505(b)(1) New Drug Application (NDA), (f) 7 year Orphan Drug Exclusivity (ODE) and (g) 12 year Biologic License Application (BLA) exclusivity.

3. USPTO patent exclusivity can be terminated prematurely if patent is held invalid and/or unenforceable. FDA marketing exclusivity is less susceptible to termination. (v11)