Legislation	Kennedy (Amdt. #)	Enzi-Hatch (Enzi Amdt. #282) (S. 1695 of the 110th Congress)	Hagan-Enzi-Hatch (Enzi Amdt. #297)	Mikulski (Amdt. #)	McCain (Amdt. #207)	Brown (Amdt. #200)
Abbreviated BLA (351(k) application)	I. Must demonstrate that the biological product and the innovator: 1. are **biosimilar** 2. use the **same mechanism of action**, if known, for the proposed labeled indications 3. use the **same route of administration, dosage form, and strength**; II. Must demonstrate that the labeled indications sought in the 351(k) have been approved for the innovator; III. Must demonstrate the facility in which the biological product is manufactured, processed, packed, or held meets cGMP; and IV. Must include publicly available information regarding the FDA's approval of innovator. ***Additional information, including a demonstration of interchangeability, may be provided.*** ***May not be filed for 4 years from the date the innovator was licensed.***	• Same as Kennedy amendment.	• Same as Kennedy amendment.	I. Must demonstrate that the biological product and the innovator: 1. are **biosimilar** 2. use the **same mechanism of action**, if known, for the proposed labeled indications 3. use the **same route of administration, dosage form, and strength**; II. Must demonstrate that the labeled indications sought in the 351(k) have been approved for the innovator; III. Must demonstrate the facility in which the biological product is manufactured, processed, packed, or held meets cGMP; and IV. Must include publicly available information regarding the FDA's approval of innovator. ***Additional information, including a demonstration of interchangeability, may be provided.***	1. Same as Kennedy amendment.	I. Must demonstrate that the biological product and the innovator: 1. are **biosimilar** 2. use the **same mechanism of action**, if known, for the proposed labeled indications 3. use the **same route of administration, dosage form, and strength**; II. Must demonstrate that the labeled indications sought in the 351(k) have been approved for the innovator; III. Must demonstrate the facility in which the biological product is manufactured, processed, packed, or held meets cGMP; and IV. Must include publicly available information regarding the FDA's approval of innovator. ***Additional information, including a demonstration of interchangeability, may be provided.***

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Biosimilarity	The 351(k) applicant must demonstrate the biological is **biosimilar *(no clinical meaningful differences exist b/w it and the innovator in terms of safety, purity, & potency)*** to the innovator through: 1. Analytical studies demonstrating it is ***highly similar to the innovator notwithstanding minor differences in clinically inactive components;*** 2. Animal studies (including a toxicity assessment); and 3. Clinical study or studies (including assessment of immunogenicity and pharmacokinetics or pharmacodynamic) demonstrating safety, purity, and potency in 1 or more appropriate conditions of use for which the innovator is licensed and intended to be used and for which licensure is sought. ****Secretary may determine these studies are unnecessary.***	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.

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Interchangeability standards	A biosimilar will be considered **interchangeable** with the innovator, meaning ***it may be substituted for the innovator without intervention of the prescribing physician,*** if it meets the following standards: 1. **Biosimilar** and can produce the **same clinical result** as the innovator in any given patient; and 2. The **risk** in terms of safety or diminished efficacy of **alternating or switching between use of the biological product and the innovator** is **not greater** than the risk of using the innovator without such alternation or switch.	• Same as Kennedy amendment.	• Same as Kennedy amendment	• Same as Kennedy amendment.	A biosimilar will be considered **interchangeable** with the innovator, meaning ***it may be substituted for the innovator without intervention of the prescribing physician,*** if it meets the following standards: 1. **Biosimilar** and can produce the **same clinical result** as the innovator in any given patient; and 2. The **risk** in terms of safety or diminished efficacy of **alternating or switching between use of the biological product and the innovator** is **not greater** than the risk of using the innovator without such alternation or switch. **Limitation:** Notwithstanding any other provisions of law, the biosimilar may only be substituted for the innovator if expressly prescribed by the physician **[this seems to conflict with the definition of interchangeability for the purpose of the amendment].**	• Same as Kennedy amendment.

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FDA evaluation of abbreviated BLA	**Reviewing division:** Same division that reviewed innovator. **Limitation:** May not be evaluated against more than 1 innovator. **Approval:** FDA shall approve if: (1) 351(k) application is sufficient to show product is **biosimilar or interchangeable** w/ the innovator; and (2) the applicant consents to facility GMP inspection	• Same as Kennedy amendment	• Same as Kennedy amendment	• Same as Kennedy amendment.	**Reviewing division:** Same division that reviewed innovator. **Limitation:** May not be evaluated against more than 1 innovator. **Approval:** FDA shall approve if: (1) 351(k) application is sufficient to show product is **biosimilar or interchangeable** w/ the innovator; (2) the applicant consents to facility GMP inspection; (3) the safety, purity, & potency of the biological is proven through **at least 1 clinical study**.	• Same as Kennedy amendment
REMS	• Applies to products approved under 351(k) applications.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.
User Fees	• Effective 10/01/2012	• Same as Kennedy amendment	• Same as Kennedy amendment	• Same as Kennedy amendment	• Same as Kennedy amendment	• Same as Kennedy amendment.
Preemption of State substitution law	• No	• None	• None	• None	• None	• No
Mandatory clinical studies	• None	• None	• None	• None	• At least 1 required for approval	• None
Product naming	• None	• None	• None	• None	• None	• None

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FDA guidance	• **Effect on 351(k) applications**: Guidance is **optional** and its issuance shall not preclude review of or action on an abbreviated BLA. • **Public comment:** required on proposed guidance and for FDA prioritization of guidance topics. • **Product class-specific guidance**: must include criteria FDA will use to determine whether a biological is "highly similar" to an innovator in such product class, and the criteria, if available, for interchangeability. • **Certain product classes**: FDA may indicate that the current science and experience with respect to a product or product class **(not including any recombinant protein)** does not allow approval for a 351(k) referencing such a product or product class.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.

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Innovator non-patent exclusivity	**Products eligible for a 9 yr exclusivity period:** 1. Certain innovators approved after enactment. 2. No major substance or highly similar major substance approved under any other BLA 3. BLA did not rely on any clinical safety, purity, or potency study in any other approved BLA or clinical safety or effectiveness study in a NDA. **3 yr. bonus period:** Supplemental BLA approved 1 year prior to expiration of initial period must: 1. contain reports of new clinical investigations; and 2. provide a ***significant therapeutic advance***, which may demonstrate safety, purity, and potency for a significant new indication or subpopulation, other than pediatric subpopulation. **1 yr. bonus period:** • Same as for first bonus period. ***Only one extension per bonus period.***	**Period:** 12 years from the date of first licensure **Limitation:** date of first licensure does not include supplemental BLAs for new indications, route of administration, dosage form, or strength of the previously licensed innovator.	**Period:** 12 years from the date of first licensure **Limitation:** The following innovator products are not entitled to the 12 year protection from approval, or the 4 year protection from the filing of a 351(k) application referencing the innovator: 1. supplemental BLAs; 2. subsequent applications filed by the innovator (or a licensor, predecessor in interest, or other related entity) for a. a change (not including a modification to the structure of the innovator) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or b. a modification to the innovator's structure that does not result in a change in safety, purity, or potency	**Period:** 10 years from the date of first licensure **1 yr. bonus period:** Supplemental BLA approved at least 2 years prior to expiration of initial exclusivity period must be approved for one or more new therapeutic indications and bring a significant clinical benefit, in comparison with existing therapies. • Benefit may be based on improved efficacy or improved safety. • Benefit shall reflect a major contribution to patient care **Limitation:** Only a new biological product that meaningfully differs from a previously-licensed biological product in molecular structure, starting materials, or manufacturing process shall be entitled to a 10-year exclusivity period when a new BLA with respect to such product is filed. ***only one extension period permitted***	**Period:** 10 years from the date of first licensure **2 yr. bonus period:** If significant therapeutic advances with respect to innovator product. **Limitation:** date of first licensure does not include supplemental BLAs for new indications, route of administration, dosage form, or strength of the previously licensed innovator.	**Products eligible for a 7 yr exclusivity period:** 1. Certain innovators approved after enactment. 2. No major substance or highly similar major substance approved under any other BLA 3. BLA did not rely on any clinical safety, purity, or potency study in any other approved BLA or clinical safety or effectiveness study in a NDA. **6 month bonus period:** Supplemental BLA approved 1 year prior to expiration of initial period must: 1. contain reports of new clinical investigations; and 2. provide a ***significant therapeutic advance***, which may demonstrate safety, purity, and potency for a significant new indication or subpopulation, other than pediatric subpopulation. **90 day reduction to bonus:** if U.S. sales exceed $1M in the CY preceding approval.

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Innovator non-patent exclusivity for new indication of existing product	**<u>Products eligible for a 2 yr base exclusivity period:</u>** 1. Innovator approved after enactment and includes a major substance approved in another BLA. 2. Innovator BLA must contain reports of new clinical investigations and provide a ***significant therapeutic advance***. **<u>3 yr. bonus period:</u>** Supplemental BLA approved 1 year prior to expiration of initial period must: 1. contain reports of new clinical investigations; and 2. provide a ***significant therapeutic advance***, which may demonstrate safety, purity, and potency for a significant new indication or subpopulation, other than pediatric subpopulation. **<u>1 yr. bonus period:</u>** • Same as for first bonus period.	• None	• None	• None	• None	**<u>Products eligible for a 3 yr base exclusivity period:</u>** 1. Innovator approved after enactment and includes a major substance approved in another BLA. 2. Innovator BLA must contain reports of new clinical investigations and provide a ***significant therapeutic advance***. **<u>6 month bonus period:</u>** Supplemental BLA approved 1 year prior to expiration of initial period must: 1. contain reports of new clinical investigations; and 2. provide a ***significant therapeutic advance***, which may demonstrate safety, purity, and potency for a significant new indication or subpopulation, other than pediatric subpopulation. **<u>90 day reduction to bonus:</u>** if U.S. sales exceed $1M in the CY preceding approval.

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Innovator non-patent exclusivity for orphan drugs	• The longer of 7 years under section 527(a) of the FFDCA or the 9 years under section 351(k) of the PHSA.	• The longer of 7 years under section 527(a) of the FFDCA or the 12 years under section 351(k) of the PHSA.	• The longer of 7 years under section 527(a) of the FFDCA or the 12 years under section 351(k) of the PHSA.	• The longer of 7 years under section 527(a) of the FFDCA or the 10 years under section 351(k) of the PHSA	• The longer of 7 years under section 527(a) of the FFDCA or the 10 years under section 351(k) of the PHSA	• 7 years.
Pediatric subpopulation studies	• Biosimilar products that are deemed interchangeable to the reference product are not subject to the requirements of 21 U.S.C. § 355c, which addresses the safety and effectiveness of the product in all relevant pediatric subpopulations, as well as the determination of dosing and administration of the product in such populations.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment	• Same as Kennedy amendment

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Innovator non-patent exclusivity for pediatric drugs	• Prior to approval of a BLA for a drug FDA determines to benefit the pediatric population, additional 6 months of market exclusivity is available if pediatric studies are conducted – this applies to supplemental and orphan drug BLAs as well. • Additional 6 months not available if determination of pediatric benefit is made later than 9 months prior to the expiration of the applicable base exclusivity period.	• None	• None	• Prior to approval of a BLA for a drug FDA determines to benefit the pediatric population, additional 6 months of market exclusivity is available if pediatric studies are conducted. o For orphan drugs, the exclusivity will be extended 2 years. • Additional exclusivity not available if determination of pediatric benefit is made later than 9 months prior to the expiration of the exclusivity period	• None	• Prior to approval of a BLA for a drug FDA determines to benefit the pediatric population, additional 6 months of market exclusivity is available if pediatric studies are conducted – this applies to supplemental and orphan drug BLAs as well. • Additional 6 months not available if determination of pediatric benefit is made later than 9 months prior to the expiration of the applicable base exclusivity period.

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Biosimilar market exclusivity	**<u>First interchangeable biosimilar</u>** – market exclusivity for a period that is the earlier of: • **<u>1 year</u>** after the first commercial marketing of such product; • **<u>18 months</u>** after a final court decision or dismissal with or without prejudice of all patent infringement action against the 351(k) applicant • **<u>42 months</u>** after approval if such patent litigation is ongoing within 42 months of such approval; or • **<u>18 months</u>** after approval, if no such patent litigation was instituted. ******FDA may determine a subsequent biological to be biosimilar and approve the abbreviated BLA even though it may not make an interchangeability determination until the exclusivity period is expired.***	**<u>First interchangeable biosimilar</u>** – market exclusivity for a period that is the earlier of: • **<u>1 year</u>** after the first commercial marketing of such product; • **<u>18 months</u>** after a final court decision or dismissal with or without prejudice of all patent infringement action against the 351(k) applicant • **<u>42 months</u>** after approval if such patent litigation is ongoing within **36 [this was likely a scrivener's error that was probably corrected to 42 in Enzi #282]** months of such approval; or • **<u>18 months</u>** after approval, if no such patent litigation was instituted.	**<u>First interchangeable biosimilar</u>** – market exclusivity for a period that is the earlier of: • **<u>1 year</u>** after the first commercial marketing of such product; • **<u>18 months</u>** after a final court decision or dismissal with or without prejudice of all patent infringement action against the 351(k) applicant • **<u>42 months</u>** after approval if such patent litigation is ongoing within 42 months of such approval; or • **<u>18 months</u>** after approval, if no such patent litigation was instituted.	**<u>First interchangeable biosimilar</u>** – market exclusivity for a period that is the earlier of: • **<u>1 year</u>** after the first commercial marketing of such product; • **<u>18 months</u>** after a final court decision or dismissal with or without prejudice of all patent infringement action against the 351(k) applicant • **<u>42 months</u>** after approval if such patent litigation is ongoing within 42 months of such approval; or • **<u>18 months</u>** after approval, if no such patent litigation was instituted.	**<u>First interchangeable biosimilar</u>** – market exclusivity for a period that is the earlier of: • **<u>1 year</u>** after the first commercial marketing of such product; • **<u>18 months</u>** after a final court decision or dismissal with or without prejudice of all patent infringement action against the 351(k) applicant • **<u>42 months</u>** after approval if such patent litigation is ongoing within 42 months of such approval; or • **<u>18 months</u>** after approval, if no such patent litigation was instituted.	• Same as Kennedy amendment.

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Resolution of Patent Disputes: Request for Information and Disclosure	**Notice of application and patent request:** W/in 20 days of notification by FDA that it will review the abbreviated BLA, the 351(k) applicant shall provide to the innovator its BLA and information that describes its manufacturing process for the biological product subject of the BLA. • Information is to remain confidential • Innovator may bring declaratory judgment against 351(k) applicant if no BLA provided. **Patent list:** W/in 60 days of receiving the BLA, the innovator shall provide the 351(k) applicant w/: 1. a list of patents on which a claim of patent infringement could reasonably be asserted, and 2. identification of the patents on the list that the innovator would be prepared to license to the 351(k) applicant. ***If patent not listed, innovator may not bring infringement claim on that patent.***	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.

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Resolution of Patent Disputes: Notice of Challenge	**Patent challenge:** W/in 60 days of receipt of the list, the 351(k) applicant: • may provide a list to the innovator of patents on which a claim of patent infringement could reasonably be asserted; • shall provide w/ respect to each patent listed by either party: 1. factual & legal arguments why a patent is invalid, unenforceable, or will not be infringed by commercial marketing; or 2. a statement indicating the applicant will not begin commercial marketing until the patent expiration, and • shall respond to the innovator regarding each patent the innovator indicated it would license to the applicant. ***Innovator may bring declaratory judgment action if no patent statement provided.***	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.

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Resolution of Patent Disputes: Infringement Suits	**Patent infringement argument:** W/in 60 days after receipt of the patent challenge, the reference product sponsor shall provide: 1. the factual and legal argument why each patent will be infringed by the commercial marketing; and 2. a response regarding validity and enforceability of the patents. **Good faith negotiations:** Both parties shall engage in good faith negotiations to agree which patents may be subject to an infringement claim – a secondary process begins if no agreement reached w/in 15 days. **Infringement suit:** Innovator must file suit w/in 30 days of an agreement that a patent is subject to an infringement claim, or w/in 30 days of the secondary list exchange. ***failure to file suit w/in 30 days limits innovator's remedy to reasonable royalties.***	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.

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Resolution of Patent Disputes: Biosimilar Launch	• **Notice:** 180 days prior to launch of biosimilar, 351(k) applicant must give notice to innovator of expected launch. • **Remedy:** Innovator may seek preliminary injunction. • **Declaratory Judgment:** If no notice of launch provided, innovator make seek declaratory judgment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.	• Same as Kennedy amendment.