

114TH CONGRESS  
1ST SESSION

# S. 1767

To amend the Federal Food, Drug, and Cosmetic Act with respect to combination products, and for other purposes.

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IN THE SENATE OF THE UNITED STATES

JULY 15, 2015

Mr. ISAKSON (for himself, Mr. CASEY, and Mr. ROBERTS) introduced the following bill; which was read twice and referred to the Committee on Health, Education, Labor, and Pensions

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## A BILL

To amend the Federal Food, Drug, and Cosmetic Act with respect to combination products, and for other purposes.

1 *Be it enacted by the Senate and House of Representa-*  
2 *tives of the United States of America in Congress assembled,*

3 **SECTION 1. SHORT TITLE.**

4 This Act may be cited as the “Combination Product  
5 Regulatory Fairness Act of 2015”.

6 **SEC. 2. DEVICE DEFINITION.**

7 Section 201(h) of the Federal Food, Drug, and Cos-  
8 metic Act (21 U.S.C. 321(h)) is amended—

9 (1) by redesignating subparagraphs (1), (2),  
10 and (3) as clauses (A), (B), and (C), respectively;

1           (2) by striking “(h)” and inserting “(h)(1)”;

2           and

3           (3) by adding at the end the following:

4           “(2)(A) Before determining that an article does not  
5 meet the definition of a device under this paragraph, the  
6 Secretary shall provide to the sponsor of the article com-  
7 petent and reliable scientific rationale that—

8           “(i) cites any scientific evidence relied upon to  
9 support the rationale; and

10           “(ii) supports such determination.

11           “(B) If the Secretary makes a determination de-  
12 scribed in clause (A)—

13           “(i) the sponsor of the article may propose a  
14 nonclinical or clinical study, limited to not more data  
15 than necessary to establish the significance, if any,  
16 of the chemical action in achieving the primary in-  
17 tended purpose of the article; and

18           “(ii) the Secretary and the sponsor of the arti-  
19 cle shall collaborate in good faith to reach agree-  
20 ment, within a reasonable time not to exceed 90  
21 days, on the design of such study.

22           “(C) The data resulting from a study conducted  
23 under clause (B) shall inform the classification of the arti-  
24 cle.”.

1 **SEC. 3. COMBINATION PRODUCTS.**

2 Section 503(g) of the Federal Food, Drug, and Cos-  
3 metic Act (21 U.S.C. 353(g)) is amended—

4 (1) by redesignating paragraphs (2) through  
5 (5) as paragraphs (6) through (9), respectively;

6 (2) by striking “(g)(1)” and all that follows  
7 through the end of paragraph (1) and inserting the  
8 following:

9 “(g)(1)(A) The Secretary shall, in accordance with  
10 this subsection, assign an agency center to regulate prod-  
11 ucts that constitute a combination of a drug, device, or  
12 biological product (referred to in this subsection as the  
13 ‘lead center’).

14 “(B) The Secretary shall conduct the premarket re-  
15 view of any combination product, whenever possible, under  
16 a single application using existing premarket review au-  
17 thorities.

18 “(C) The Secretary shall determine the primary mode  
19 of action of the combination product. If the Secretary de-  
20 termines that the primary mode of action is that of—

21 “(i) a drug (other than a biological product),  
22 the agency center charged with premarket review of  
23 drugs shall have primary jurisdiction;

24 “(ii) a device, the agency center charged with  
25 premarket review of devices shall have primary juris-  
26 diction; or

1           “(iii) a biological product, the agency center  
2           charged with premarket review of biological products  
3           shall have primary jurisdiction.

4           “(D) In determining the primary mode of action of  
5           a combination product, the Secretary shall not determine  
6           that the primary mode of action is that of a drug or bio-  
7           logical product solely because the combination product has  
8           any chemical action within or on the human body.

9           “(E) If the Secretary disagrees with the conclusions  
10          of the sponsor on the primary mode of action of the com-  
11          bination product, the Secretary shall provide a competent  
12          and reliable scientific rationale to the product sponsor that  
13          cites any scientific evidence relied upon to support the de-  
14          cision.

15          “(F) For purposes of this paragraph—

16                 “(i) the term ‘primary mode of action’ means  
17                 the single mode of action of a combination product  
18                 that provides the most important therapeutic action  
19                 of the combination product; and

20                 “(ii) the term ‘most important therapeutic ac-  
21                 tion’ means the mode of action expected to make the  
22                 greatest contribution to the overall intended thera-  
23                 peutic effects of the combination product.

24          “(2)(A) The sponsor of a combination product may  
25          submit a combination product review plan (referred to in

1 this subsection as a ‘CPRP’) for the combination product,  
2 and may request a meeting prior to submission of the  
3 CPRP, to establish clarity and certainty for the sponsor  
4 regarding the standards and requirements applicable to—

5 “(i) the review of safety and effectiveness, or  
6 substantial equivalence, of the combination product;

7 “(ii) a postmarket modification of the combina-  
8 tion product; or

9 “(iii) good manufacturing practices for the com-  
10 bination product.

11 “(B) Not later than 60 days after the sponsor of a  
12 combination product submits a proposed CPRP, including  
13 a revision to a previously proposed or approved CPRP,  
14 the Secretary shall review the CPRP and—

15 “(i) if the Secretary determines that the CPRP  
16 is appropriate to ensure adequate review of the safe-  
17 ty and effectiveness, or substantial equivalence, of  
18 the combination product—

19 “(I) approve the CPRP; and

20 “(II) issue to the sponsor a response indi-  
21 cating such approval; or

22 “(ii) if the Secretary finds that the CPRP does  
23 not meet the standard specified in clause (i)—

24 “(I) decline to approve the CPRP; and

1           “(II) issue to the sponsor a response indi-  
2           cating that the Secretary has declined such ap-  
3           proval and specifying any deficiencies in the  
4           proposed CPRP.

5           “(C)(i) In the case of a CPRP that the Secretary de-  
6           clines to approve under subparagraph (B)(ii), unless the  
7           sponsor submitting such CPRP determines a meeting is  
8           not necessary, the Secretary shall, not later than 30 days  
9           after submitting a response under such subparagraph,  
10          meet with such sponsor to discuss the CPRP.

11          “(ii) A meeting under clause (i) shall—

12                  “(I) include any necessary experts from the rel-  
13                  evant agency centers; and

14                  “(II) coordinate the advice of such experts.

15          “(D) The sponsor or applicant shall provide informa-  
16          tion necessary for discussion and agreement on the level  
17          of evidence necessary to ensure adequate review of the  
18          safety and effectiveness, or substantial equivalence, of the  
19          combination product.

20          “(E) Not later than 30 days after the date on which  
21          a meeting is held under subparagraph (A)(i), the minutes  
22          of such meeting shall be prepared by the sponsor and  
23          made available to the Secretary.

24          “(F) Any agreement that is reached between the Sec-  
25          retary and a sponsor or applicant through a meeting held

1 under subparagraph (A)(i) shall be reduced to writing by  
2 the sponsor or applicant, and, once approved by the Sec-  
3 retary, made part of the administrative record by the Sec-  
4 retary within 60 days of such meeting.

5 “(G) An agreement described in subparagraph (F)  
6 shall not be changed after approval of the agreement, ex-  
7 cept—

8 “(i) with the written agreement of the sponsor  
9 or applicant; or

10 “(ii) pursuant to a decision, made in accordance  
11 with subparagraph (H) by the director of the review-  
12 ing division of the lead center, in consultation with  
13 consulting centers and the Office, that a substantial  
14 scientific issue essential to determining the safety or  
15 effectiveness, or substantial equivalence, of the com-  
16 bination product has been identified.

17 “(H) With respect to a decision under subparagraph  
18 (G)(ii), the Secretary shall provide notice, within 2 busi-  
19 ness days of such decision, to the sponsor of the combina-  
20 tion product and an opportunity for a meeting to take  
21 place not later than 14 calendar days after issuing such  
22 notice, at which—

23 “(i) the director of the reviewing division of the  
24 lead center, staff from the consulting agency centers,

1 representatives of the Office, and the sponsor will be  
2 present; and

3 “(ii) the director of the reviewing division of the  
4 lead center will document the scientific issue in-  
5 volved.

6 “(3) For purposes of conducting the premarket re-  
7 view of a combination product that contains an approved  
8 constituent product described in paragraph (4), the Sec-  
9 retary may require only that the sponsor of such combina-  
10 tion product submit to the Secretary data or information  
11 that—

12 “(A) the Secretary determines is necessary to  
13 assess the specific safety and effectiveness questions  
14 and incremental risks posed by the combination  
15 product, using a risk-based approach and taking into  
16 account any prior finding of safety and efficacy or  
17 substantial equivalence for the approved constituent  
18 product; and

19 “(B) is not duplicative of data or information  
20 included in an application or other material sub-  
21 mitted to the Secretary in connection with the ap-  
22 proved constituent product.

23 “(4) For purposes of paragraph (3), an approved con-  
24 stituent product is—

1           “(A) a drug constituent part of a combination  
2 product being reviewed in a single application under  
3 section 515 or 510(k), provided such drug con-  
4 stituent part was previously approved under section  
5 505 and such application complies with subpara-  
6 graph (A) of paragraph (5) and is subject to sub-  
7 paragraphs (D) and (E) of such paragraph;

8           “(B) a device constituent part approved under  
9 section 515 that is referenced by the sponsor and  
10 which is available for use by the Secretary under  
11 section 520(h)(4); or

12           “(C) any constituent part that was previously  
13 approved, cleared, or licensed under section 505,  
14 510(k), or 515 of this Act or section 351 of the  
15 Public Health Service Act, for which the sponsor has  
16 a right of reference or which is otherwise available  
17 for consideration by the Secretary under this Act or  
18 the Public Health Service Act.

19           “(5)(A) If an application is submitted under section  
20 515 or 510(k) for a combination product containing as  
21 a constituent part an approved drug—

22           “(i) the application shall include the certifi-  
23 cation or statement required pursuant section  
24 505(b)(2); and

1           “(ii) the applicant shall provide notice as re-  
2           quired pursuant to section 505(b)(3).

3           “(B) For purposes of this paragraph, the term ‘ap-  
4           proved drug’ means a drug—

5           “(i) that was previously approved under section  
6           505;

7           “(ii) for which full reports of investigations that  
8           have been made to show whether such drug is safe  
9           for use and whether such drug is effective in use—

10           “(I) are relied upon by the applicant sub-  
11           mitting the application described in subpara-  
12           graph (A); and

13           “(II) were not conducted by or for such  
14           applicant; and

15           “(iii) with respect to which, the applicant sub-  
16           mitting the application described in subparagraph  
17           (A) has not obtained a right of reference or use from  
18           the person by or for whom the investigations were  
19           conducted.

20           “(C) The following provisions shall apply with respect  
21           an application described in subparagraph (A):

22           “(i) Subparagraphs (A), (B), (C), and (D) of  
23           section 505(c)(3).

24           “(ii) Clauses (ii), (iii), and (iv) of section  
25           505(c)(3)(E).

1           “(iii) Paragraphs (b) and (c) of section 505A.

2           “(iv) Section 505E(a).

3           “(v) Section 527(a).

4           “(D) Notwithstanding section 520(h)(4)(A)(i), infor-  
5 mation contained in an application for premarket approval  
6 filed with the Secretary pursuant to section 515(c) may  
7 not be used to approve any application submitted under  
8 section 515 or 510(k) for a combination product con-  
9 taining as a constituent part a drug previously approved  
10 under section 505 unless—

11           “(i) the application includes the certification or  
12 statement referenced in subparagraph (A);

13           “(ii) the applicant provides notice as described  
14 in subparagraph (A); and

15           “(iii) the Secretary’s approval of such applica-  
16 tion is subject to the provisions specified in subpara-  
17 graph (C).

18           “(E) An application for a combination product de-  
19 scribed in subparagraph (A) or (D) shall be considered  
20 an application submitted under Section 505(b)(2) solely  
21 for purposes of section 271(e)(2)(A) of the Patent Act.”;

22           (3) in paragraph (8) (as redesignated by para-  
23 graph (1))—

24           (A) in subparagraph (C)—

1 (i) by amending clause (i) to read as  
2 follows:

3 “(i) In carrying out this subsection, the Office shall  
4 ensure timely and effective premarket reviews involving  
5 more than one agency center by—

6 “(I) overseeing the timeliness and alignment of  
7 reviews; and

8 “(II) coordinating reviews.”;

9 (ii) in clause (ii), by inserting “and  
10 alignment” after “the timeliness” each  
11 place it appears; and

12 (iii) by adding at the end the fol-  
13 lowing new clauses:

14 “(iii) The Office shall ensure that the lead center be  
15 the primary point of contact for the sponsor of the prod-  
16 uct. The Office shall also coordinate communications to  
17 and from any consulting agency center involved in such  
18 premarket review. Agency communications and commit-  
19 ments, to the extent consistent with other provisions of  
20 law and the requirements of all affected agency centers,  
21 from the lead center shall be binding on all other centers  
22 involved in the review.

23 “(iv) The Office shall, with respect to the premarket  
24 review of a combination product—

1           “(I) ensure that any meeting between the Food  
2           and Drug Administration and the sponsor of the  
3           product is attended by each agency center involved  
4           in the review, as appropriate;

5           “(II) require that each consulting agency center  
6           has completed its premarket review and provided the  
7           results of such review to the lead center within time-  
8           frames that allow the lead center to meet the review  
9           goals established pursuant to the most recent au-  
10          thorization or reauthorization of parts 2, 3, 7, and  
11          8, as applicable, of subchapter C of title VII; and

12          “(III) ensure that each consulting agency cen-  
13          ter complies with the guidance described in clause  
14          (vi) and other relevant regulations, guidances, and  
15          policies.

16          “(v) Not later than 10 days after the receipt by an  
17          agency center of an application under section 505, 510(k),  
18          or 520 of this Act, or under section 351 of the Public  
19          Health Service Act, for a combination product or an appli-  
20          cation for investigational use of a combination product  
21          under section 505(i) or 520(g), the agency center shall  
22          inform the Office of such receipt.

23          “(vi) Not later than 2 years after the date of enact-  
24          ment of the Combination Product Regulatory Fairness Act  
25          of 2015, the Secretary shall issue final guidance that de-

1 scribes the responsibilities of each agency center regarding  
2 its review of combination products, including each center’s  
3 role in evaluating evidence development and review under  
4 a risk-based approach, dispute resolution, labeling, prod-  
5 uct usability assessments, and human factors testing. The  
6 Office shall, after soliciting public comment, review and  
7 update the guidance at least biannually and specify in  
8 such updated guidance the reasons for updates.”;

9 (B) in subparagraph (E)—

10 (i) by striking clause (i) and inserting  
11 the following new clause:

12 “(i) During the review process, any dispute regarding  
13 the substance, timeliness, review process, requirements, or  
14 alignment of the premarket review may be presented to  
15 the Office for resolution and the Office shall convene the  
16 relevant parties and resolve conflicts not later than 90  
17 days after the date on which the Office receives written  
18 notice of such conflicts.”; and

19 (ii) in clause (ii), by striking “During  
20 the review process, any dispute regarding  
21 the substance of the premarket review”  
22 and inserting “Any remaining dispute”;

23 (C) in subparagraph (F), in the first sen-  
24 tence—

1 (i) by inserting “or which involves de-  
2 termining the safety or efficacy of a com-  
3 ponent of a combination product” after  
4 “assignment of combination products to  
5 agency centers”; and

6 (ii) by inserting “and with the guid-  
7 ance described in subparagraph (C)(vi).”  
8 before the period at the end; and

9 (D) in subparagraph (G)—

10 (i) in clause (ii), by striking “and” at  
11 the end;

12 (ii) in clause (iii), by striking the pe-  
13 riod at the end and inserting a semicolon;  
14 and

15 (iii) by adding at the end the fol-  
16 lowing new clauses:

17 “(iv) identifying the percentage of combination  
18 products for which a dispute resolution, with respect  
19 to premarket review, was requested by the combina-  
20 tion product’s sponsor; and

21 “(v) identifying the percentage of meetings be-  
22 tween the Food and Drug Administration and the  
23 sponsor of a combination product at which all of the  
24 centers participating in the review of the combina-

1       tion product were in attendance, in accordance with  
2       subparagraph (C)(iv)(I).”;

3               (4) in paragraph (9) (as redesignated by para-  
4       graph (1)), by adding at the end the following:

5               “(D) The terms ‘premarket review’ and ‘re-  
6       views’ include all activities of the Food and Drug  
7       Administration conducted prior to approval or clear-  
8       ance of an application or notification submitted  
9       under section 505, 510(k), 515, or 520 of this Act  
10       or under section 351 of the Public Health Service  
11       Act, including with respect to investigational use of  
12       the product.”; and

13               (5) by adding at the end the following:

14               “(10) RULE OF CONSTRUCTION.—Nothing in this  
15       subsection shall be construed as prohibiting a sponsor, at  
16       the sponsor’s discretion, from submitting separate applica-  
17       tions for the constituent parts of a combination product,  
18       unless the Secretary determines that a single application  
19       is necessary to ensure the safety and effectiveness, or sub-  
20       stantial equivalence, as applicable, of the combination  
21       product.”.

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