

Calendar No. 414

114TH CONGRESS
2D SESSION**S. 1767**

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

IN THE SENATE OF THE UNITED STATES

JULY 15, 2015

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

APRIL 5, 2016

Reported by Mr. ALEXANDER, with an amendment

[Strike out all after the enacting clause and insert the part printed in italic]

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”.

1 **SEC. 2. DEVICE DEFINITION.**

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

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

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

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

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

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

15 “(ii) supports such determination.

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

18 “(i) the sponsor of the article may propose a
19 nonclinical or clinical study, limited to not more data
20 than necessary to establish the significance, if any,
21 of the chemical action in achieving the primary in-
22 tended purpose of the article; and

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

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

4 **SEC. 3. COMBINATION PRODUCTS.**

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

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

9 (2) by striking “(g)(1)” and all that follows
 10 through the end of paragraph (1) and inserting the
 11 following:

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

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

21 “(C) The Secretary shall determine the primary mode
 22 of action of the combination product. If the Secretary de-
 23 termines that the primary mode of action is that of—

1 “(i) a drug (other than a biological product);
2 the agency center charged with premarket review of
3 drugs shall have primary jurisdiction;

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

7 “(iii) a biological product, the agency center
8 charged with premarket review of biological products
9 shall have primary jurisdiction.

10 “(D) In determining the primary mode of action of
11 a combination product, the Secretary shall not determine
12 that the primary mode of action is that of a drug or bio-
13 logical product solely because the combination product has
14 any chemical action within or on the human body.

15 “(E) If the Secretary disagrees with the conclusions
16 of the sponsor on the primary mode of action of the com-
17 bination product, the Secretary shall provide a competent
18 and reliable scientific rationale to the product sponsor that
19 cites any scientific evidence relied upon to support the de-
20 cision.

21 “(F) For purposes of this paragraph—

22 “(i) the term ‘primary mode of action’ means
23 the single mode of action of a combination product
24 that provides the most important therapeutic action
25 of the combination product; and

1 “(ii) the term ‘most important therapeutic ac-
2 tion’ means the mode of action expected to make the
3 greatest contribution to the overall intended thera-
4 peutic effects of the combination product.

5 “(2)(A) The sponsor of a combination product may
6 submit a combination product review plan (referred to in
7 this subsection as a ‘CPRP’) for the combination product;
8 and may request a meeting prior to submission of the
9 CPRP, to establish clarity and certainty for the sponsor
10 regarding the standards and requirements applicable to—

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

13 “(ii) a postmarket modification of the combina-
14 tion product; or

15 “(iii) good manufacturing practices for the com-
16 bination product.

17 “(B) Not later than 60 days after the sponsor of a
18 combination product submits a proposed CPRP, including
19 a revision to a previously proposed or approved CPRP,
20 the Secretary shall review the CPRP and—

21 “(i) if the Secretary determines that the CPRP
22 is appropriate to ensure adequate review of the safe-
23 ty and effectiveness, or substantial equivalence, of
24 the combination product—

25 “(I) approve the CPRP; and

1 “(H) issue to the sponsor a response indi-
2 cating such approval; or

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

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

6 “(H) issue to the sponsor a response indi-
7 cating that the Secretary has declined such ap-
8 proval and specifying any deficiencies in the
9 proposed CPRP.

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

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

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

19 “(H) coordinate the advice of such experts.

20 “(D) The sponsor or applicant shall provide informa-
21 tion necessary for discussion and agreement on the level
22 of evidence necessary to ensure adequate review of the
23 safety and effectiveness, or substantial equivalence, of the
24 combination product.

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

5 “(F) Any agreement that is reached between the Sec-
6 retary and a sponsor or applicant through a meeting held
7 under subparagraph (A)(i) shall be reduced to writing by
8 the sponsor or applicant, and, once approved by the Sec-
9 retary, made part of the administrative record by the Sec-
10 retary within 60 days of such meeting.

11 “(G) An agreement described in subparagraph (F)
12 shall not be changed after approval of the agreement, ex-
13 cept—

14 “(i) with the written agreement of the sponsor
15 or applicant; or

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

23 “(H) With respect to a decision under subparagraph
24 (G)(ii), the Secretary shall provide notice, within 2 busi-
25 ness days of such decision, to the sponsor of the combina-

1 tion product and an opportunity for a meeting to take
2 place not later than 14 calendar days after issuing such
3 notice, at which—

4 “(i) the director of the reviewing division of the
5 lead center, staff from the consulting agency centers,
6 representatives of the Office, and the sponsor will be
7 present; and

8 “(ii) the director of the reviewing division of the
9 lead center will document the scientific issue in-
10 volved.

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

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

24 “(B) is not duplicative of data or information
25 included in an application or other material sub-

1 mitted to the Secretary in connection with the ap-
 2 proved constituent product.

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

5 ~~“(A) a drug constituent part of a combination~~
 6 product being reviewed in a single application under
 7 section ~~515~~ or ~~510(k)~~, provided such drug con-
 8 stituent part was previously approved under section
 9 ~~505~~ and such application complies with subpara-
 10 graph (A) of paragraph (5) and is subject to sub-
 11 paragraphs (D) and (E) of such paragraph;

12 ~~“(B) a device constituent part approved under~~
 13 section ~~515~~ that is referenced by the sponsor and
 14 which is available for use by the Secretary under
 15 section ~~520(h)(4)~~; or

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

23 ~~“(5)(A) If an application is submitted under section~~
 24 ~~515~~ or ~~510(k)~~ for a combination product containing as
 25 a constituent part an approved drug—

1 “(i) the application shall include the certifi-
2 cation or statement required pursuant section
3 505(b)(2); and

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

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

8 “(i) that was previously approved under section
9 505;

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

13 “(I) are relied upon by the applicant sub-
14 mitting the application described in subpara-
15 graph (A); and

16 “(II) were not conducted by or for such
17 applicant; and

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

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

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

3 “(ii) Clauses (ii), (iii), and (iv) of section
4 505(c)(3)(E).

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

6 “(iv) Section 505E(a).

7 “(v) Section 527(a).

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

15 “(i) the application includes the certification or
16 statement referenced in subparagraph (A);

17 “(ii) the applicant provides notice as described
18 in subparagraph (A); and

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

22 “(E) An application for a combination product de-
23 scribed in subparagraph (A) or (D) shall be considered
24 an application submitted under Section 505(b)(2) solely
25 for purposes of section 271(c)(2)(A) of the Patent Act.”;

1 ~~(3)~~ in paragraph ~~(8)~~ (as redesignated by para-

2 graph ~~(1)~~)—

3 ~~(A)~~ in subparagraph ~~(C)~~—

4 (i) by amending clause (i) to read as

5 follows:

6 “(i) In carrying out this subsection, the Office shall

7 ensure timely and effective premarket reviews involving

8 more than one agency center by—

9 “(I) overseeing the timeliness and alignment of

10 reviews; and

11 “(II) coordinating reviews.”;

12 (ii) in clause (ii), by inserting “and

13 alignment” after “the timeliness” each

14 place it appears; and

15 (iii) by adding at the end the fol-

16 lowing new clauses:

17 “(iii) The Office shall ensure that the lead center be

18 the primary point of contact for the sponsor of the prod-

19 uct. The Office shall also coordinate communications to

20 and from any consulting agency center involved in such

21 premarket review. Agency communications and commit-

22 ments, to the extent consistent with other provisions of

23 law and the requirements of all affected agency centers,

24 from the lead center shall be binding on all other centers

25 involved in the review.

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

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

7 “(II) require that each consulting agency center
8 has completed its premarket review and provided the
9 results of such review to the lead center within time-
10 frames that allow the lead center to meet the review
11 goals established pursuant to the most recent au-
12 thorization or reauthorization of parts 2, 3, 7, and
13 8, as applicable, of subchapter C of title VII; and

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

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

1 “(vi) Not later than 2 years after the date of enact-
 2 ment of the Combination Product Regulatory Fairness Act
 3 of 2015, the Secretary shall issue final guidance that de-
 4 scribes the responsibilities of each agency center regarding
 5 its review of combination products, including each center’s
 6 role in evaluating evidence development and review under
 7 a risk-based approach, dispute resolution, labeling, prod-
 8 uct usability assessments, and human factors testing. The
 9 Office shall, after soliciting public comment, review and
 10 update the guidance at least biannually and specify in
 11 such updated guidance the reasons for updates.”;

12 (B) in subparagraph (E)—

13 (i) by striking clause (i) and inserting
 14 the following new clause:

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

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

(C) in subparagraph (F), in the first sentence—

(i) by inserting “or which involves determining the safety or efficacy of a component of a combination product” after “assignment of combination products to agency centers”; and

(ii) by inserting “and with the guidance described in subparagraph (C)(vi).” before the period at the end; and

(D) in subparagraph (G)—

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

(ii) in clause (iii), by striking the period at the end and inserting a semicolon; and

(iii) by adding at the end the following new clauses:

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

“(v) identifying the percentage of meetings between the Food and Drug Administration and the sponsor of a combination product at which all of the

centers participating in the review of the combination product were in attendance, in accordance with subparagraph (C)(iv)(I).”;

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

“(D) The terms ‘premarket review’ and ‘reviews’ include all activities of the Food and Drug Administration conducted prior to approval or clearance of an application or notification submitted under section 505, 510(k), 515, or 520 of this Act or under section 351 of the Public Health Service Act, including with respect to investigational use of the product.”; and

(5) by adding at the end the following:

“(10) RULE OF CONSTRUCTION.—Nothing in this subsection shall be construed as prohibiting a sponsor, at the sponsor’s discretion, from submitting separate applications for the constituent parts of a combination product, unless the Secretary determines that a single application is necessary to ensure the safety and effectiveness, or substantial equivalence, as applicable, of the combination product.”.

SECTION 1. SHORT TITLE.

This Act may be cited as the “Combination Product Regulatory Fairness Act of 2016”.

1 **SEC. 2. COMBINATION PRODUCTS.**

2 (a) *IN GENERAL.*—Section 503(g) of the Federal Food,
3 Drug, and Cosmetic Act (21 U.S.C. 353(g)) is amended—

4 (1) by striking paragraph (3);

5 (2) by redesignating paragraph (2) as para-
6 graph (7);

7 (3) by redesignating paragraphs (4) and (5) as
8 paragraphs (8) and (9), respectively; and

9 (4) by striking “(g)(1)” and all that follows
10 through the end of paragraph (1) and inserting the
11 following:

12 “(g)(1)(A) The Secretary shall, in accordance with this
13 subsection, assign a primary agency center to regulate
14 products that constitute a combination of a drug, device,
15 or biological product.

16 “(B) The Secretary shall conduct the premarket review
17 of any combination product under a single application,
18 whenever appropriate.

19 “(C) For purposes of this subsection, the term ‘primary
20 mode of action’ means the single mode of action of a com-
21 bination product expected to make the greatest contribution
22 to the overall intended therapeutic effects of the combination
23 product.

24 “(D) The Secretary shall determine the primary mode
25 of action of the combination product. If the Secretary deter-
26 mines that the primary mode of action is that of—

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

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

7 “(iii) a biological product, the agency center
8 charged with premarket review of biological products
9 shall have primary jurisdiction.

10 “(E) In determining the primary mode of action of
11 a combination product, the Secretary shall not determine
12 that the primary mode of action is that of a drug or biologi-
13 cal product solely because the combination product has any
14 chemical action within or on the human body.

15 “(F) If a sponsor of a combination product disagrees
16 with the determination under subparagraph (D)—

17 “(i) such sponsor may request, and the Secretary
18 shall provide, a substantive rationale to such sponsor
19 that references scientific evidence provided by the
20 sponsor and any other scientific evidence relied upon
21 by the Secretary to support such determination; and

22 “(ii)(I) the sponsor of the combination product
23 may propose one or more studies (which may be non-
24 clinical, clinical, or both) to establish the relevance, if

1 *any, of the chemical action in achieving the primary*
2 *mode of action of such product;*

3 *“(II) if the sponsor proposes any such studies,*
4 *the Secretary and the sponsor of such product shall*
5 *collaborate and seek to reach agreement, within a rea-*
6 *sonable time of such proposal, not to exceed 90 cal-*
7 *endar days, on the design of such studies; and*

8 *“(III) if an agreement is reached under sub-*
9 *clause (II) and the sponsor conducts one or more of*
10 *such studies, the Secretary shall consider the data re-*
11 *sulting from any such study when reevaluating the*
12 *determination of the primary mode of action of such*
13 *product, and unless and until such reevaluation has*
14 *occurred and the Secretary issues a new determina-*
15 *tion, the determination of the Secretary under sub-*
16 *paragraph (D) shall remain in effect.*

17 *“(2)(A)(i) To establish clarity and certainty for the*
18 *sponsor, the sponsor of a combination product may submit*
19 *a proposed combination product review plan with respect*
20 *to such combination product, at any point following the*
21 *Secretary’s determination of the primary mode of action*
22 *pursuant to paragraph (1).*

23 *“(ii) Such proposed combination product review plan*
24 *may—*

1 “(I) address the standards and requirements for
2 market approval or clearance of the combination
3 product;

4 “(II) address other issues relevant to such com-
5 bination product, such as requirements related to
6 postmarket modification of such combination product
7 and good manufacturing practices applicable to such
8 combination product; and

9 “(III) identify elements under subclauses (I) and
10 (II) that may be more appropriate for discussion and
11 agreement with the Secretary at a later date given
12 that scientific or other information is not available,
13 or agreement is otherwise not feasible regarding such
14 elements, at the time such plan is submitted.

15 “(B) After the sponsor of a combination product sub-
16 mits a proposed combination product review plan under
17 subparagraph (A), the Secretary shall review such plan
18 and, in a written response to such sponsor—

19 “(i) accept such plan in its entirety, which may
20 include elements to be the subject of discussion and
21 agreement between the sponsor and the Secretary at
22 a later date, as described in subparagraph
23 (A)(ii)(III);

24 “(ii) accept the plan in part, which may include
25 elements that have not been accepted at the time of the

1 *response and are to be the subject of discussion and*
 2 *agreement between the sponsor and the Secretary at*
 3 *a later date, as described in subparagraph*
 4 *(A)(ii)(III), and elements that the Secretary declines*
 5 *to accept; or*

6 *“(iii) deny such plan in its entirety.*

7 *“(C) When reviewing a proposed combination product*
 8 *review plan under subparagraph (B), the Secretary shall*
 9 *accept such plan, or elements of such plan, if the Secretary*
 10 *determines that the data to be collected is appropriate—*

11 *“(i) for market approval or clearance of the com-*
 12 *bination product; or*

13 *“(ii) to otherwise meet relevant standards under*
 14 *this Act, as applicable.*

15 *“(D)(i) If the Secretary declines to accept a proposed*
 16 *combination product review plan under subparagraph*
 17 *(B)(iii), or elements of such a plan under subparagraph*
 18 *(B)(ii), the Secretary shall, in the written response to such*
 19 *sponsor—*

20 *“(I) include a description of the deficiencies of*
 21 *such plan or such elements, as applicable; and*

22 *“(II) clarify what elements may be suitable for*
 23 *discussion at a later date.*

24 *“(ii) If the Secretary declines to accept a proposed*
 25 *combination product review plan under subparagraph*

1 *(B)(iii), or elements of such a plan under subparagraph*
 2 *(B)(ii), the sponsor of such plan may request a meeting*
 3 *with the Secretary. Upon the request of the sponsor, the Sec-*
 4 *retary, including any necessary experts from the relevant*
 5 *agency centers, shall meet with the sponsor to discuss a pro-*
 6 *posed combination product review plan or elements of a*
 7 *combination product review plan that the Secretary has de-*
 8 *clined to accept, for the purpose of discussing the informa-*
 9 *tion and requirements necessary to make the plan or ele-*
 10 *ments of such plan acceptable. Minutes of such meeting shall*
 11 *be made part of the administrative record.*

12 *“(iii) If the Secretary declines to accept a proposed*
 13 *combination product review plan under subparagraph*
 14 *(B)(iii), or elements of such a plan under subparagraph*
 15 *(B)(ii), a sponsor may resubmit a proposed combination*
 16 *product review plan for consideration by the Secretary*
 17 *under subparagraph (A).*

18 *“(E) A combination product review plan accepted*
 19 *under subparagraph (B)(i), or the elements of a combina-*
 20 *tion product review plan that are accepted under subpara-*
 21 *graph (B)(ii), shall remain in effect, except—*

22 *“(i) with the written agreement of the Secretary*
 23 *and the sponsor or applicant; or*

24 *“(ii) pursuant to a decision, made in accordance*
 25 *with subparagraph (F) by the director of the review-*

1 *ing division of the primary agency center, or a per-*
2 *son more senior than such director, in consultation*
3 *with consulting centers and the Office, that an impor-*
4 *tant, materially relevant scientific issue essential to*
5 *determining the safety or effectiveness, or substantial*
6 *equivalence, as applicable, of the combination product*
7 *has been identified since a combination product re-*
8 *view plan or elements of a combination product re-*
9 *view plan were accepted, as applicable.*

10 *“(F) If the Secretary makes a decision under subpara-*
11 *graph (E)(ii), the Secretary shall provide notice, within a*
12 *reasonable time after such decision, to the sponsor of the*
13 *combination product subject to such decision and provide*
14 *an opportunity for a meeting with the Secretary, to take*
15 *place within a reasonable time after issuing such notice,*
16 *at which—*

17 *“(i) the director of the reviewing division of the*
18 *primary agency center, or a person more senior than*
19 *such director, staff from the consulting centers, rep-*
20 *resentatives of the Office, and the sponsor shall be rep-*
21 *resented; and*

22 *“(ii) the director of the reviewing division of the*
23 *primary agency center, or a person more senior than*
24 *the director, shall describe the important, materially*
25 *relevant issue involved to such sponsor.*

1 “(3) *For purposes of conducting the premarket review*
2 *of a combination product that contains an approved con-*
3 *stituent part described in paragraph (4), the Secretary may*
4 *require that the sponsor of such combination product sub-*
5 *mit to the Secretary only data or information that the Sec-*
6 *retary determines is necessary to assess the safety and effec-*
7 *tiveness of the combination product, including any incre-*
8 *mental risks and benefits posed by such combination prod-*
9 *uct, using a risk-based approach and taking into account*
10 *any prior finding of safety and effectiveness or substantial*
11 *equivalence for the approved constituent part relied upon*
12 *by the applicant in accordance with paragraph (5).*

13 “(4) *For purposes of paragraph (3), an approved con-*
14 *stituent part is—*

15 “(A) *a drug constituent part of a combination*
16 *product being reviewed in a single application or re-*
17 *quest under section 515, 510(k), or 513(f)(2) (sub-*
18 *mitted in accordance with paragraph (5)), that is an*
19 *approved drug, provided such application or request*
20 *complies with paragraph (5);*

21 “(B) *a device constituent part approved under*
22 *section 515 that is referenced by the sponsor and that*
23 *is available for use by the Secretary under section*
24 *520(h)(4); or*

1 “(C) any constituent part that was previously
2 approved, cleared, or classified under section 505,
3 510(k), 513(f)(2), or 515 of this Act for which the
4 sponsor has a right of reference or any constituent
5 part that is a nonprescription drug, as defined in sec-
6 tion 760(a)(2).

7 “(5)(A) If an application is submitted under section
8 515, 510(k), or a request is submitted under section
9 513(f)(2), consistent with any determination made under
10 paragraph (1)(D), for a combination product containing as
11 a constituent part an approved drug—

12 “(i) the application or request shall include the
13 certification or statement described in section
14 505(b)(2); and

15 “(ii) the applicant or requester shall provide no-
16 tice as described in section 505(b)(3).

17 “(B) For purposes of this paragraph and paragraph
18 (4), the term ‘approved drug’ means an active ingredient—

19 “(i) that was in an application previously ap-
20 proved under section 505(c);

21 “(ii) where such application is relied upon by
22 the applicant submitting the application or request
23 described in subparagraph (A);

24 “(iii) for which full reports of investigations that
25 have been made to show whether such drug is safe for

1 *use and whether such drug is effective in use were not*
2 *conducted by or for the applicant submitting the ap-*
3 *plication or request described in subparagraph (A);*
4 *and*

5 *“(iv) for which the applicant submitting the ap-*
6 *plication or request described in subparagraph (A)*
7 *has not obtained a right of reference or use from the*
8 *person by or for whom the investigations described in*
9 *clause (iii) were conducted.*

10 *“(C) The following provisions shall apply with respect*
11 *to an application or request described in subparagraph (A)*
12 *to the same extent and in the same manner as if such appli-*
13 *cation or request were an application described in section*
14 *505(b)(2) that referenced the approved drug:*

15 *“(i) Subparagraphs (A), (B), (C), and (D) of*
16 *section 505(c)(3).*

17 *“(ii) Clauses (ii), (iii), and (iv) of section*
18 *505(c)(3)(E).*

19 *“(iii) Subsections (b) and (c) of section 505A.*

20 *“(iv) Section 505E(a).*

21 *“(v) Section 527(a).*

22 *“(D) Notwithstanding any other provision of this sub-*
23 *section, an application or request for classification for a*
24 *combination product described in subparagraph (A) shall*
25 *be considered an application submitted under section*

1 505(b)(2) for purposes of section 271(e)(2)(A) of title 35,
 2 United States Code.

3 “(6) Nothing in this subsection shall be construed as
 4 prohibiting a sponsor from submitting separate applica-
 5 tions for the constituent parts of a combination product,
 6 unless the Secretary determines that a single application
 7 is necessary.”;

8 (5) in paragraph (8) (as redesignated by para-
 9 graph (3))—

10 (A) in subparagraph (C)—

11 (i) by amending clause (i) to read as
 12 follows:

13 “(i) In carrying out this subsection, the Office shall
 14 help to ensure timely and effective premarket review that
 15 involves more than one agency center by coordinating such
 16 reviews, overseeing the timeliness of such reviews, and over-
 17 seeing the alignment of feedback regarding such reviews.”;

18 (ii) in clause (ii), by inserting “and
 19 alignment” after “the timeliness” each place
 20 it appears; and

21 (iii) by adding at the end the following
 22 new clauses:

23 “(iii) The Office shall ensure that, with respect to a
 24 combination product, a designated person or persons in the
 25 primary agency center be the primary point or points of

1 *contact for the sponsor of such combination product. The*
 2 *Office shall also coordinate communications to and from*
 3 *any consulting center involved in such premarket review,*
 4 *if requested by such primary agency center or any such con-*
 5 *sulting center. Agency communications and commitments,*
 6 *to the extent consistent with other provisions of law and*
 7 *the requirements of all affected agency centers, from the pri-*
 8 *mary agency center shall be considered as communication*
 9 *from the Food and Drug Administration on behalf of all*
 10 *agency centers involved in the review.*

11 “(iv) *The Office shall, with respect to the premarket*
 12 *review of a combination product—*

13 “(I) *ensure that any meeting between the Food*
 14 *and Drug Administration and the sponsor of such*
 15 *product is attended by each agency center involved in*
 16 *the review, as appropriate;*

17 “(II) *ensure that each consulting agency center*
 18 *has completed its premarket review and provided the*
 19 *results of such review to the primary agency center in*
 20 *a timely manner; and*

21 “(III) *ensure that each consulting center follows*
 22 *the guidance described in clause (vi) and advises, as*
 23 *appropriate, on other relevant regulations, guidances,*
 24 *and policies.*

1 “(v) *In seeking agency action with respect to a com-*
2 *bination product, the sponsor of such product—*

3 “(I) *shall identify the product as a combination*
4 *product; and*

5 “(II) *may request in writing the participation of*
6 *representatives of the Office in meetings related to*
7 *such combination product, or to have the Office other-*
8 *wise engage on such regulatory matters concerning*
9 *the combination product.*

10 “(vi) *Not later than 4 years after the date of enactment*
11 *of the Combination Product Regulatory Fairness Act of*
12 *2016, and after a public comment period of not less than*
13 *60 calendar days, the Secretary shall issue a final guidance*
14 *that describes—*

15 “(I) *the responsibilities of each agency center re-*
16 *garding its review of combination products, including*
17 *each center’s role in evaluating evidence development*
18 *and review under a risk-based approach, dispute reso-*
19 *lution, labeling, product usability assessments, and*
20 *human factors testing;*

21 “(II) *the structured process for managing pre-*
22 *submission interactions with sponsors developing*
23 *combination products;*

24 “(III) *the best practices for ensuring that the*
25 *feedback in such pre-submission interactions rep-*

1 resents the Agency’s best advice based on the informa-
 2 tion provided during such pre-submission inter-
 3 actions;

4 “(IV) the best practices regarding submissions by
 5 sponsors, and review by the Secretary, of combination
 6 product review plans under paragraph (2), including
 7 the appropriate timing for discussion and agreement
 8 of such plans, and the various elements of such plans,
 9 based on scientific and technical understanding dur-
 10 ing product development;

11 “(V) the Secretary’s processes for ensuring input
 12 from experts from each relevant agency center in such
 13 pre-submission interactions with sponsors developing
 14 combination products and in fulfilling the require-
 15 ments of this subsection;

16 “(VI) the timelines associated with responding
 17 to, and holding meetings regarding, combination
 18 product review plans under paragraph (2); and

19 “(VII) disputes appropriate for presentation to
 20 the Office as described in subparagraph (E)(i).”.

21 (B) in subparagraph (E)—

22 (i) by striking clause (i) and inserting
 23 the following new clause:

24 “(i) During the review process, disputes between dif-
 25 ferent agency centers regarding the substance, timeliness, re-

1 *view process, requirements, or alignment of the premarket*
 2 *review with respect to a combination product, including*
 3 *conflicting feedback, responses, and decisions from such*
 4 *agency centers, may be presented to the Office by the spon-*
 5 *sor of such combination product for resolution and the Of-*
 6 *fice shall convene the relevant parties and seek to resolve*
 7 *such conflicts.”; and*

8 *(ii) in clause (ii), by striking “During*
 9 *the review process, any dispute regarding*
 10 *the substance of the premarket review” and*
 11 *inserting “Any dispute remaining after the*
 12 *process under clause (i) is completed”;*

13 *(C) in subparagraph (F), in the first sen-*
 14 *tence—*

15 *(i) by inserting “or that involves deter-*
 16 *mining the safety or efficacy, reasonable as-*
 17 *surance of safety and efficacy, or substan-*
 18 *tial equivalence of a component of a com-*
 19 *bination product” after “assignment of*
 20 *combination products to agency centers”;*
 21 *and*

22 *(ii) by inserting “and with the guid-*
 23 *ance described in subparagraph (C)(vi)” be-*
 24 *fore the period at the end; and*

25 *(D) in subparagraph (G)—*

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

3 (ii) in clause (iii), by striking the pe-
4 riod at the end and inserting a semicolon;
5 and

6 (iii) by adding at the end the following
7 new clauses:

8 “(iv) identifying the percentage of combination
9 products for which a dispute resolution, with respect
10 to premarket review, was requested by the combina-
11 tion product’s sponsor;

12 “(v) stating the average, median, and range of
13 response times to combination product review plans
14 under paragraph (2);

15 “(vi) identifying the percentage of meetings be-
16 tween the Food and Drug Administration and the
17 sponsor of a combination product at which all of the
18 agency centers participating in the review of the com-
19 bination product were in attendance, in accordance
20 with subparagraph (C)(iv)(I); and

21 “(vii) for the report submitted in 2017, and in
22 a report at least once every 5 years thereafter, regard-
23 ing any recommendations to streamline premarket re-
24 view of combination products.”; and

(6) in paragraph (9) (as redesignated by paragraph (3))—

(A) in subparagraph (C)—

(i) in clause (ii), by striking “and”;

(ii) in clause (iii), by striking the period and inserting “, and”; and

(iii) by adding at the end the following:

“(iv) *de novo* classification under section 513(a)(1).”; and

(B) by adding at the end the following:

“(D) The terms ‘premarket review’ and ‘reviews’ include all activities of the Food and Drug Administration conducted prior to approval or clearance of an application, notification, or request for classification submitted under section 505, 510(k), 513(f)(2), 515, or 520 of this Act or under section 351 of the Public Health Service Act, including with respect to investigational use of the product.”.

(b) *INFORMATION FOR APPROVAL OF COMBINATION PRODUCTS.*—Section 520(h)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360j) is amended—

(1) in subparagraph (A), by striking “Any information” and inserting “Subject to subparagraph (C), any information”; and

1 (2) *by adding at the end the following new sub-*
 2 *paragraph:*

3 “(C) *No information contained in an appli-*
 4 *cation for premarket approval filed with the Sec-*
 5 *retary pursuant to section 515(c) may be used to*
 6 *approve or clear any application submitted*
 7 *under section 515 or 510(k) or to classify a prod-*
 8 *uct under section 513(f)(2) for a combination*
 9 *product containing as a constituent part an*
 10 *“approved drug” as defined in section*
 11 *503(g)(5)(B) unless—*

12 “(i) *the application includes the cer-*
 13 *tification or statement referenced in section*
 14 *503(g)(5)(A);*

15 “(ii) *the applicant provides notice as*
 16 *described in Section 503(g)(5)(A); and*

17 “(iii) *the Secretary’s approval of such*
 18 *application is subject to the provisions in*
 19 *section 503(g)(5)(C).”.*

20 (c) *VARIATIONS FROM CGMP STREAMLINED AP-*
 21 *PROACH.—Not later than 18 months after the date of enact-*
 22 *ment of this Act, the Secretary shall identify types of com-*
 23 *bination products that the Secretary proposes may adopt*
 24 *good manufacturing practices that vary from the require-*
 25 *ments set forth in section 4.4 of title 21, Code of Federal*

1 *Regulations (or any successor regulations). The Secretary*
2 *shall identify such types, and identify variations from such*
3 *requirements, in a proposed list published in the Federal*
4 *Register. After a public comment period regarding the ap-*
5 *propriate good manufacturing practices for such types, the*
6 *Secretary shall publish a final list in the Federal Register,*
7 *notwithstanding section 553 of title 5, United States Code.*
8 *The Secretary shall evaluate such types and such appro-*
9 *priate variations using a risk-based approach. The Sec-*
10 *retary shall periodically review such types on such final*
11 *list, including whether additional types of combination*
12 *products are appropriate for such final list.*

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114TH CONGRESS
2^D Session

S. 1767

A BILL

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

APRIL 5, 2016

Reported with an amendment