

*Mike Braun*  
**Amendment #3**

AMENDMENT NO. \_\_\_\_\_ Calendar No. \_\_\_\_\_

Purpose: To establish a time-limited provisional approval pathway, subject to specific obligations, for certain drugs and biological products.

**IN THE SENATE OF THE UNITED STATES—117th Cong., 2d Sess.**

**S. 4348**

To amend the Federal Food, Drug, and Cosmetic Act to revise and extend the user-fee programs for prescription drugs, medical devices, generic drugs, and biosimilar biological products, and for other purposes.

Referred to the Committee on \_\_\_\_\_ and  
ordered to be printed

Ordered to lie on the table and to be printed

AMENDMENT intended to be proposed by Mr. BRAUN (for  
himself and Ms. MURKOWSKI)

Viz:

1 At the appropriate place in title V, insert the fol-  
2 lowing:

3 **SEC. 5 \_\_\_\_ . PROVISIONAL APPROVAL OF NEW HUMAN**  
4 **DRUGS.**

5 (a) **SHORT TITLE.**—This section may be cited as the  
6 “Promising Pathway Act”.

7 (b) **ESTABLISHMENT OF PRIORITY REVIEW SYS-**  
8 **TEM.**—Subchapter A of chapter V of the Federal Food,  
9 Drug, and Cosmetic Act (21 U.S.C. 351 et seq.) is amend-  
10 ed by adding at the end of the following:

1 **"SEC. 524B. PROVISIONAL APPROVAL OF NEW HUMAN**  
2 **DRUGS.**

3 **"(a) PRIORITY REVIEW AND EVALUATION OF APPLI-**  
4 **CATIONS.—**

5 **"(1) IN GENERAL.—**The Secretary shall estab-  
6 lish a priority review system to evaluate applications  
7 submitted under this pathway for provisional ap-  
8 proval within 90 days of receipt of a completed ap-  
9 plication.

10 **"(2) OTHER DESIGNATIONS.—**If a drug sub-  
11 mitted for review under the pathway under this sec-  
12 tion is eligible for a special designation by the Sec-  
13 retary under this Act, including as a drug for a rare  
14 disease or condition under section 526, all benefits  
15 of such other designation shall be available for use  
16 under provisional approval, including any tax credits  
17 and waiving of fees under chapter VII.

18 **"(b) ELIGIBILITY.—**A drug may be eligible for provi-  
19 sional approval under this section if the Secretary deter-  
20 mines that the drug is intended for the treatment, preven-  
21 tion, or medical diagnosis of a serious or life-threatening  
22 disease or condition for which there is a reasonable likeli-  
23 hood that premature death will occur without early med-  
24 ical intervention for an individual contracting or being di-  
25 agnosed with such disease or condition.

26 **"(c) STANDARD OF REVIEW FOR APPROVAL.—**

1           “(1) REQUIREMENTS.—An application for pro-  
2           visional approval under this section may be approved  
3           only if the Secretary determines that—

4                   “(A) there is substantial evidence of safety  
5                   for the drug, such that there is evidence con-  
6                   sisting of adequate and well-controlled inves-  
7                   tigations, including clinical investigations, by  
8                   experts qualified by scientific training and expe-  
9                   rience to evaluate the safety of the drug in-  
10                  volved, on the basis of which it could fairly and  
11                  responsibly be concluded that the drug will have  
12                  the effect it purports or is represented to have  
13                  under the conditions of use prescribed, rec-  
14                  ommended, or suggested in the labeling or pro-  
15                  posed labeling; and

16                   “(B) there is relevant early evidence based  
17                   on adequate and well-controlled investigations,  
18                   including early-stage clinical investigations, to  
19                   establish that—

20                           “(i) the drug provides a positive  
21                           therapeutic outcome; and

22                           “(ii) if there are currently marketed  
23                           on-label therapies for the applicable disease  
24                           or condition—

1                   “(I) the outcome of the drug is  
2                   consistent with such on-label therapies  
3                   and produces fewer side effects; or

4                   “(II) the outcome of the drug is  
5                   greater than such on-label therapies  
6                   and produces equal or fewer side ef-  
7                   fects.

8                   “(2) PROTOCOLS.—The Secretary shall promul-  
9                   gate rules that establish the appropriate protocols  
10                  for a sponsor of an application for provisional ap-  
11                  proval under this section and the Commissioner to  
12                  follow to enable rolling, real-time, mid-trial submis-  
13                  sion while preserving the integrity of the ongoing  
14                  trial and without penalizing the sponsor for making  
15                  use of this pathway.

16                  “(3) REAL WORLD EVIDENCE.—The Secretary  
17                  shall allow the use of real world evidence (as defined  
18                  in section 505F(b)), including real world data used  
19                  to generate real world evidence, to support an appli-  
20                  cation for provisional approval under this section,  
21                  and to fulfill the follow-up requirements and support  
22                  applications for full approval as described under sec-  
23                  tion 505 or section 351 of the Public Health Service  
24                  Act, as applicable.

1           “(4) USE OF SCIENTIFICALLY-SUBSTANTIATED  
2 SURROGATES.—

3           “(A) IN GENERAL.—The sponsor of an ap-  
4 plication for provisional approval under this sec-  
5 tion may use scientifically-substantiated surro-  
6 gates to support such application.

7           “(B) DEFINITION.—In subparagraph (A),  
8 the term ‘scientifically-substantiated surrogates’  
9 means surrogate endpoints to predict clinical  
10 benefit other than such endpoints previously  
11 validated by the Secretary, based on—

12           “(i) epidemiologic, therapeutic, patho-  
13 physiologic, or other evidence; or

14           “(ii) an effect on a clinical endpoint  
15 other than survival or irreversible mor-  
16 bidity of interest.

17           “(d) TRANSPARENCY AND PATIENT MONITORING  
18 REQUIREMENTS.—

19           “(1) REGISTRIES.—

20           “(A) IN GENERAL.—The sponsor of a drug  
21 provisionally approved under this section shall  
22 require that all patients who use such drug par-  
23 ticipate in an observational registry and consent  
24 to the sponsor’s collection, and submission to  
25 the registry, of data related to the patient’s use

1 of such drug until such drug receives full ap-  
2 proval under section 505 or section 351 of the  
3 Public Health Service Act, or the provisional  
4 approval is rescinded.

5 “(B) REQUIREMENTS FOR REGISTRIES.—  
6 An observational registry described in subpara-  
7 graph (A) may be run by a third party, such as  
8 a government, for profit, or non-profit organiza-  
9 tion, and shall track all patients who use the  
10 provisionally approved drug.

11 “(C) ACCESSIBILITY.—An observational  
12 registry described in subparagraph (A) shall be  
13 easily accessible for—

14 “(i) all patients who are participating  
15 in any registry related to a provisionally  
16 approved drug that allows for easy, unre-  
17 stricted (or transparent) access for such  
18 patients to their patient data and related  
19 information regarding their usage of the  
20 provisionally approved drug; and

21 “(ii) approved researchers and med-  
22 ical professionals who may access data  
23 maintained in the registry, which access  
24 shall be for public health research and only  
25 in a de-identified, aggregated manner.

1           “(D) MINIMUM NECESSARY STANDARD.—

2           When using or disclosing protected health infor-  
3           mation or when requesting protected health in-  
4           formation from another entity, a sponsor of a  
5           drug provisionally approved under this section,  
6           or a third party that runs the observational reg-  
7           istry pursuant to subparagraph (B), shall make  
8           reasonable efforts to limit protected health in-  
9           formation to the minimum necessary to accom-  
10          plish the intended purpose of the use, disclo-  
11          sure, or request. Such requirement shall not  
12          apply to—

13               “(i) disclosures to, or requests by, a  
14               health care provider for treatment;

15               “(ii) uses or disclosures made to the  
16               patient; or

17               “(iii) uses or disclosures made to the  
18               Secretary.

19           “(E) USES AND DISCLOSURES OF DE-  
20          IDENTIFIED PROTECTED HEALTH INFORMA-  
21          TION.—

22               “(i) IN GENERAL.—A sponsor of a  
23               drug provisionally approved under this sec-  
24               tion may use protected health information  
25               to create information that is not individ-

1 ually identifiable health information and  
2 that does not involve the disclosure of pro-  
3 tected health information to a third party,  
4 such as a government, for-profit, or non-  
5 profit organization, or individuals de-  
6 scribed in subparagraph (C), regardless of  
7 whether the de-identifiable information is  
8 to be used by such organizations or indi-  
9 viduals.

10 “(ii) INFORMATION THAT IS NOT IN-  
11 DIVIDUALLY IDENTIFIABLE HEALTH IN-  
12 FORMATION.—For purposes of this sub-  
13 section, health information that meets the  
14 standard and implementation specifications  
15 for de-identification under subsections (a)  
16 and (b) of section 164.514 of title 45,  
17 Code of Federal Regulations (or any suc-  
18 cessor regulation) shall not be considered  
19 to be individually identifiable health infor-  
20 mation.

21 “(iii) REQUIREMENTS NOT TO  
22 APPLY.—The requirements under subpara-  
23 graph (D) shall not apply if—

24 “(I) the information is a code or  
25 other means of record identification



1 designed to enable coded or otherwise  
2 de-identified information to be re-  
3 identified; and

4 “(II) the information is de-identi-  
5 fied information that is re-identified,  
6 and the information is accessible only  
7 by a third party pursuant to a con-  
8 tract or agreement with the drug  
9 sponsor consistent with the terms of  
10 the contract or agreement.

11 “(F) DECEASED INDIVIDUALS.—A sponsor  
12 of a drug provisionally approved under this sec-  
13 tion shall comply with the requirements under  
14 this paragraph with respect to the protected  
15 health information of a deceased individual for  
16 a period of 50 years following the death of the  
17 individual. An executor, administrator, or other  
18 person has authority to act on behalf of a de-  
19 ceased individual or of the individual’s estate,  
20 and shall be treated as a personal representa-  
21 tive under this subparagraph, with respect to  
22 protected health information relevant to such  
23 personal representation.

24 “(G) RULE OF CONSTRUCTION.—Nothing  
25 in this paragraph shall be construed to limit the

1 access of an individual who is a subject of re-  
2 search to information about himself or herself  
3 collected during such individual's participation  
4 in the research and while receiving a drug that  
5 has been provisionally approved under this sec-  
6 tion.

7 “(2) FUNDING.—An observational registry  
8 under this subsection shall be maintained, as appli-  
9 cable—

10 “(A) by the sponsor of the drug provision-  
11 ally approved under this section that is the sub-  
12 ject of the registry; or

13 “(B) by a third party, such as a govern-  
14 ment, for profit, or nonprofit organization.

15 “(3) SPONSOR REQUIREMENTS.—

16 “(A) IN GENERAL.—For any drug applica-  
17 tion provisionally approved under this section,  
18 the Secretary shall notify the sponsor of the  
19 exact data such sponsor is required to submit  
20 to an observational registry.

21 “(B) ANNUAL REVIEW OF THE REGISTRY;  
22 PENALTIES.—The Secretary shall conduct an  
23 annual review of observational registries estab-  
24 lished under this subsection. If, at such an an-  
25 nual review, less than 90 percent of patients are

1 participating in an observational registry with  
2 respect to a drug approved under this section,  
3 the Secretary shall notify the sponsor of such  
4 drug and issue to the sponsor a civil monetary  
5 penalty of not more than \$100,000. If a viola-  
6 tion of this section is not corrected within the  
7 30-day period following notification, the sponsor  
8 shall, in addition to any penalty under this sub-  
9 paragraph be subject to a civil monetary pen-  
10 alty of not more than \$10,000 for each day of  
11 the violation after such period until the viola-  
12 tion is corrected. If application patient partici-  
13 pation in an observational registry is not at or  
14 above 90 percent within 6 months of issuance  
15 of such penalty, the provisional approval shall  
16 be withdrawn.

17 “(4) PATIENT PRIVACY.—

18 “(A) INFORMED CONSENT.—Prior to re-  
19 ceiving a drug provisionally approved under this  
20 section, the sponsor of the drug shall receive  
21 from each patient, or the patient’s representa-  
22 tive, explicit and affirmative informed consent,  
23 through a signed informed consent form, ac-  
24 knowledging that such patient understands that  
25 the drug did not undergo the usual process for

1 full approval of a drug by the Food and Drug  
2 Administration, and that such patient is willing  
3 to accept the risks involved in taking such drug.  
4 The informed consent form shall meet the fol-  
5 lowing requirements:

6 “(i) Such form shall include the fol-  
7 lowing:

8 “(I) An exhaustive list of the  
9 types of research that may be con-  
10 ducted with the identifiable private in-  
11 formation or identifiable biospecimens,  
12 and descriptions of the type of re-  
13 search.

14 “(II) A description of the identi-  
15 fiable private information or identifi-  
16 able biospecimens that might be used  
17 in research, whether sharing of identi-  
18 fiable private information or identifi-  
19 able biospecimens might occur, and  
20 the types of institutions or researchers  
21 that might conduct the research with  
22 the identifiable private information or  
23 identifiable biospecimens.

24 “(III) A description of the period  
25 of time that the identifiable private

1 information or identifiable biospeci-  
2 mens may be stored and maintained,  
3 and a description of the period of time  
4 that the identifiable private informa-  
5 tion or identifiable biospecimens may  
6 be used for research purposes.

7 “(IV) An explanation of whom to  
8 contact for answers to questions about  
9 the subject’s rights and about storage  
10 and use of the subject’s identifiable  
11 private information or identifiable bio-  
12 specimens, and whom to contact in  
13 the event of a research-related injury  
14 to the subject.

15 “(V) An exhaustive list of the  
16 types of specified types of information  
17 from the patient’s medical record that  
18 may be used for research purposes.

19 “(ii) Such form shall be formatted to  
20 allow patients to explicitly consent or opt-  
21 in to the types of medical data collected.

22 “(iii) Such form shall specify the du-  
23 ration of time for which the drug sponsor  
24 will collect the data.

1                   “(iv) Such form shall specify who will  
2                   have access to the patient’s data.

3                   “(v) Such form shall not grant the  
4                   drug sponsor open access to the patient’s  
5                   medical record, unless explicitly stated in  
6                   the informed consent form and the patient  
7                   provides explicit consent.

8                   “(vi) Such form may not be formatted  
9                   in a way that requires the patient to dis-  
10                  sent or opt-out of any information in-  
11                  tended for collection or review by the drug  
12                  sponsor.

13                  “(vii) A sponsor of a drug provision-  
14                  ally approved under this section may not  
15                  use or disclose protected health informa-  
16                  tion for research by obtaining documenta-  
17                  tion that an alteration to, or waiver of, in  
18                  whole or part, the patient’s informed con-  
19                  sent has been approved by an Institutional  
20                  Review Board or a privacy board.

21                  “(B) LIMITATIONS.—The sponsor of a  
22                  drug provisionally approved under this sec-  
23                  tion—

24                         “(i) shall have access to the informa-  
25                         tion the patient has agreed to in the in-

1           formed consent described in subparagraph  
2           (A) from the date the patient has signed  
3           the informed consent form until 10 years  
4           after the date the provisional approval of  
5           the drug has expired or the drug provision-  
6           ally approved under this section has re-  
7           ceived full market approval;

8           “(ii) shall delete or de-identify sen-  
9           sitive personal data, and shall direct its  
10          service providers to delete or de-identify  
11          sensitive personal data—

12               “(I) after the data is no longer  
13               reasonably necessary to accomplish  
14               the intended purposes permitted by  
15               this section, unless deletion or de-  
16               identification is impossible or demon-  
17               strably impracticable; or

18               “(II) 10 years after the date the  
19               provisional approval of the drug has  
20               expired or the drug provisionally ap-  
21               proved under this section has received  
22               full market approval;

23               “(iii) shall de-identify and aggregate  
24               information related to patients receiving  
25               provisionally approved drugs when sharing

1 information with any person not included  
2 on the informed consent form signed by  
3 the patient, or the patient's representative;  
4 "(iv) may not receive waived consent  
5 from any institution, or institutional review  
6 board, to collect information related to a  
7 patient receiving a provisionally approved  
8 drug under this section;  
9 "(v) may not receive broad consent  
10 for the storage, maintenance, or secondary  
11 research use of identifiable private infor-  
12 mation or identifiable biospecimens as an  
13 alternative to informed consent;  
14 "(vi) may not appeal to an institu-  
15 tional review board to waive the require-  
16 ment to obtain informed consent for re-  
17 search or approve a consent procedure that  
18 omits some, or alters some or all, of the  
19 elements of informed consent;  
20 "(vii) may not sell patient's protected  
21 health information, except sale of protected  
22 health information shall not include a dis-  
23 closure of protected health information for  
24 research purposes where the only remu-  
25 neration received by the covered entity or



1 business associate is a reasonable cost-  
2 based fee to cover the cost to prepare and  
3 transmit that protect health information  
4 for such purposes; and

5 “(viii) may not collect any patient in-  
6 formation not included in the informed  
7 consent form signed by the patient, or the  
8 patient’s representative, without the drug  
9 sponsor receiving secondary informed con-  
10 sent from the patient to collect data for  
11 which the patient opts-in.

12 “(e) WITHDRAWAL OF PROVISIONAL APPROVAL.—

13 “(1) IN GENERAL.—The Secretary shall with-  
14 draw provisional approval under this section if there  
15 are a significant numbers of patients who experience  
16 serious adverse effects, compared to the other cur-  
17 rently marketed on-label therapies that are available  
18 for the applicable disease or condition.

19 “(2) EFFECT OF WITHDRAWAL.—If a provi-  
20 sional approval is withdrawn under this subsection,  
21 the sponsor may not make the drug available to any  
22 new patients, but may be allowed to continue to  
23 make such drug available to patients who started  
24 taking the drug prior to the date of withdrawal, for

1 as long a period as dictated by patient need, as de-  
2 termined by the Secretary.

3 “(f) POSTMARKET CONTROLS AND LABELING.—

4 “(1) FDA ANNUAL REVIEW OF REGISTRY  
5 DATA.—The Secretary shall annually review the data  
6 made available through the observational registries  
7 under subsection (d) and make a determination re-  
8 garding whether the side effect profile of any drug  
9 approved under this pathway does not support the  
10 benefit provided, or the data shows the benefit is  
11 less than the benefits offered through other, fully-ap-  
12 proved drugs.

13 “(2) LABELING.—The sponsor of the provision-  
14 ally approved drug shall ensure that all labeling and  
15 promotional materials for the drug bear the state-  
16 ment ‘provisionally approved by the FDA pending a  
17 full demonstration of effectiveness under application  
18 number \_\_\_\_\_’ (specifying the application  
19 number assigned by the Secretary in place of the  
20 blank). All promotional, educational and marketing  
21 materials for provisionally approved products shall  
22 be reviewed and approved by the Secretary before  
23 such materials are distributed.

24 “(3) RESCISSION OF PROVISIONAL AP-  
25 PROVAL.—If the Secretary determines that the side

1 effect profile of any drug included in such observa-  
2 tional registries does not support the benefit pro-  
3 vided by such drug, or that the data shows that the  
4 benefit is less than the benefits offered through  
5 other, fully-approved drugs, the Secretary shall re-  
6 scind such provisional approval.

7 “(g) DURATION OF PROVISIONAL APPROVAL; RE-  
8 QUIREMENT TO BRING DRUG TO MARKET.—

9 “(1) DURATION; RENEWALS.—The period of  
10 provisional approval for a drug approved under this  
11 section is effective for a 2-year period. The sponsor  
12 may request renewal for provisional approval status  
13 for up to 3 subsequent 2-year periods by the Sec-  
14 retary. Provisional approval status with respect to a  
15 drug shall not exceed a total of 6 years from the ini-  
16 tial date the sponsor was awarded provisional ap-  
17 proval status.

18 “(2) MARKETING REQUIREMENT.—If any drug  
19 that receives provisional approval status under this  
20 section is not brought to market within 180 days of  
21 the approval, such approval shall be rescinded.

22 “(h) APPLYING FOR FULL APPROVAL.—

23 “(1) IN GENERAL.—Except as provided under  
24 paragraph (2), the sponsor of a drug granted provi-  
25 sional approval pursuant to this section may, at any

1 point, submit an application for full approval of such  
2 drug under section 505 of this Act or section 351  
3 of the Public Health Service Act, as applicable.

4 “(2) EFFECT OF RECESSION ON APPROVAL AND  
5 AUTOMATIC APPROVAL.—

6 “(A) IN GENERAL.—The sponsor of a drug  
7 granted provisional approval pursuant to this  
8 section that has been rescinded under sub-  
9 section (h)(3), may submit an application for  
10 full approval of such drug under section 505 of  
11 this Act or section 351 of the Public Health  
12 Service Act at any time.

13 “(B) AUTOMATIC APPROVAL.—Such full  
14 approval may be awarded at any time for any  
15 drug granted provisional approval pursuant to  
16 this section if the sponsor of the drug estab-  
17 lishes a 15 percent improvement in an impor-  
18 tant endpoint, including surrogate endpoints  
19 not validated by the Food and Drug Adminis-  
20 tration, compared to a standard drug.”.