(B) by striking "in the trial," and inserting "in the trial, and a description of whether, and through what procedure, the manufacturer or sponsor of the investigation of a new drug will respond to requests for protocol exception, with appropriate safeguards, for single-patient and expanded protocol use of the new drug, particularly in children,".

(d) REPORT.—Not later than January 31, 2003, the Secretary of Health and Human Services, acting through the Commissioner of Food and Drugs and in consultation with the Director of the National Institutes of Health, shall submit to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives a report on patient access to new therapeutic agents for pediatric cancer, including access to single patient use of new therapeutic agents.

SEC. 16. REPORT ON PEDIATRIC EXCLUSIVITY PROGRAM.

Not later than October 1, 2006, the Comptroller General of the United States, in consultation with the Secretary of Health and Human Services, shall submit to Congress a report that addresses the following issues, using publicly available data or data otherwise available to the Government that may be used and disclosed under applicable law:

(1) The effectiveness of section 505A of the Federal Food, Drug, and Cosmetic Act and section 409I of the Public Health Service Act (as added by this Act) in ensuring that medicines used by children are tested and properly labeled, including—

(A) the number and importance of drugs for children that are being tested as a result of this legislation and the importance for children, health care providers, parents, and others of labeling changes made as a result of such testing;

(B) the number and importance of drugs for children that are not being tested for their use notwithstanding the provisions of this legislation, and possible reasons for the lack of testing; and

(C) the number of drugs for which testing is being done, exclusivity granted, and labeling changes required, including the date pediatric exclusivity is granted and the date labeling changes are made and which labeling changes required the use of the dispute resolution process established pursuant to the amendments made by this Act, together with a description of the outcomes of such process, including a description of the disputes and the recommendations of the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee.

(2) The economic impact of section 505A of the Federal Food, Drug, and Cosmetic Act and section 409I of the Public Health Service Act (as added by this Act), including an estimate of—

(A) the costs to taxpayers in the form of higher expenditures by medicaid and other Government programs;

(B) sales for each drug during the 6-month period for which exclusivity is granted, as attributable to such exclusivity;

(C) costs to consumers and private insurers as a result of any delay in the availability of lower cost generic equivalents of drugs tested and granted exclusivity under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.), and loss of revenue by the generic drug industry and retail pharmacies as a result of any such delay; and

(D) the benefits to the government, to private insurers, and to consumers resulting from decreased health care costs, including—

(i) decreased hospitalizations and fewer medical errors, due to more appropriate and more effective use of medications in children as a result of testing and re-labeling because of the amendments made by this Act;

(ii) direct and indirect benefits associated with fewer physician visits not related to hospitalization;

(iii) benefits to children from missing less time at school and being less affected by chronic illnesses, thereby allowing a better quality of life;

(iv) benefits to consumers from lower health insurance premiums due to lower treatment costs and hospitalization rates; and

(v) benefits to employers from reduced need for employees to care for family members.

(3) The nature and type of studies in children for each drug granted exclusivity under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.), including—

(A) a description of the complexity of the studies;

(B) the number of study sites necessary to obtain appropriate data;

(C) the number of children involved in any clinical studies; and

(D) the estimated cost of each of the studies.

(4) Any recommendations for modifications to the programs established under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) and section 409I of the Public Health Service Act (as added by section 3) that the Secretary determines to be appropriate, including a detailed rationale for each recommendation.

(5) The increased private and Government-funded pediatric research capability associated with this Act and the amendments made by this Act.

(6) The number of written requests and additional letters of recommendation that the Secretary issues.

(7) The prioritized list of off-patent drugs for which the Secretary issues written requests.

(8)(A) The efforts made by the Secretary to increase the number of studies conducted in the neonate population; and

(B) the results of those efforts, including efforts made to encourage the conduct of appropriate studies in neonates by companies with products that have sufficient safety and other information to make the conduct of studies ethical and safe.

SEC. 17. ADVERSE-EVENT REPORTING.

(a) TOLL-FREE NUMBER IN LABELING.—Not later than one year after the date of the enactment of this Act, the Secretary of Health and Human Services shall promulgate a final rule requiring that

the labeling of each drug for which an application is approved under section 505 of the Federal Food, Drug, and Cosmetic Act (regardless of the date on which approved) include the toll-free number maintained by the Secretary for the purpose of receiving reports of adverse events regarding drugs and a statement that such number is to be used for reporting purposes only, not to receive medical advice. With respect to the final rule:

(1) The rule shall provide for the implementation of such labeling requirement in a manner that the Secretary considers to be most likely to reach the broadest consumer audience.

(2) In promulgating the rule, the Secretary shall seek to minimize the cost of the rule on the pharmacy profession.

(3) The rule shall take effect not later than 60 days after the date on which the rule is promulgated.

(b) DRUGS WITH PEDIATRIC MARKET EXCLUSIVITY.—

(1) IN GENERAL.—During the one year beginning on the date on which a drug receives a period of market exclusivity under 505A of the Federal Food, Drug, and Cosmetic Act, any report of an adverse event regarding the drug that the Secretary of Health and Human Services receives shall be referred to the Office of Pediatric Therapeutics established under section 6 of this Act. In considering the report, the Director of such Office shall provide for the review of the report by the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee, including obtaining any recommendations of such subcommittee regarding whether the Secretary should take action under the Federal Food, Drug, and Cosmetic Act in response to the report.

(2) RULE OF CONSTRUCTION.—Paragraph (1) may not be construed as restricting the authority of the Secretary of Health and Human Services to continue carrying out the activities described in such paragraph regarding a drug after the one-year period described in such paragraph regarding the drug has expired.

SEC. 18. MINORITY CHILDREN AND PEDIATRIC-EXCLUSIVITY PROGRAM.

(a) PROTOCOLS FOR PEDIATRIC STUDIES.—Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) is amended in subsection (d)(2) by inserting after the first sentence the following: "In reaching an agreement regarding written protocols, the Secretary shall take into account adequate representation of children of ethnic and racial minorities.".

(b) STUDY BY GENERAL ACCOUNTING OFFICE.—

(1) IN GENERAL.—The Comptroller General of the United States shall conduct a study for the purpose of determining the following:

(A) The extent to which children of ethnic and racial minorities are adequately represented in studies under section 505A of the Federal Food, Drug, and Cosmetic Act; and to the extent ethnic and racial minorities are not adequately represented, the reasons for such under representation and recommendations to increase such representation.

(B) Whether the Food and Drug Administration has appropriate management systems to monitor the representation of the children of ethnic and racial minorities in such studies.

(C) Whether drugs used to address diseases that disproportionately affect racial and ethnic minorities are being studied for their safety and effectiveness under section 505A of the Federal Food, Drug, and Cosmetic Act.

(2) DATE CERTAIN FOR COMPLETING STUDY.—Not later than January 10, 2003, the Comptroller General shall complete the study required in paragraph (1) and submit to the Congress a report describing the findings of the study.

SEC. 19. TECHNICAL AND CONFORMING AMENDMENTS.

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) (as amended by sections 2(1), 5(b)(2), 9, 10, 11, and 17) is amended—

(1)(A) by striking "(j)(4)(D)(ii)" each place it appears and inserting "(j)(5)(D)(ii)";

(B) by striking "(j)(4)(D)" each place it appears and inserting "(j)(5)(D)"; and

(C) by striking "505(j)(4)(D)" each place it appears and inserting "505(j)(5)(D)";

(2) by redesignating subsections (a), (g), (h), (i), (j), (k), (l), (m), (n), and (o) as subsections (b), (a), (g), (h), (n), (m), (i), (j), (k), and (l) respectively;

(3) by moving the subsections so as to appear in alphabetical order;

(4) in paragraphs (1), (2), and (3) of subsection (d), subsection (e), and subsection (m) (as redesignated by paragraph (2)), by striking "subsection (a) or (c)" and inserting "subsection (b) or (c)"; and

(5) in subsection (g) (as redesignated by paragraph (2)), by striking "subsection (a) or (b)" and inserting "subsection (b) or (c)".

Speaker of the House of Representatives.

Vice President of the United States and
President of the Senate.

S. 650

One Hundred Eighth Congress of the United States of America

AT THE FIRST SESSION

Begun and held at the City of Washington on Tuesday, the seventh day of January, two thousand and three

An Act

To amend the Federal Food, Drug, and Cosmetic Act to authorize the Food and Drug Administration to require certain research into drugs used in pediatric patients.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Pediatric Research Equity Act of 2003".

SEC. 2. RESEARCH INTO PEDIATRIC USES FOR DRUGS AND BIOLOGICAL PRODUCTS.

(a) IN GENERAL.—Subchapter A of chapter V of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351 et seq.) is amended by inserting after section 505A the following:

"SEC. 505B. RESEARCH INTO PEDIATRIC USES FOR DRUGS AND BIOLOGICAL PRODUCTS.

"(a) NEW DRUGS AND BIOLOGICAL PRODUCTS.—

"(1) IN GENERAL.—A person that submits an application (or supplement to an application)—

"(A) under section 505 for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration; or

"(B) under section 351 of the Public Health Service Act (42 U.S.C. 262) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration;

shall submit with the application the assessments described in paragraph (2).

"(2) ASSESSMENTS.—

"(A) IN GENERAL.—The assessments referred to in paragraph (1) shall contain data, gathered using appropriate formulations for each age group for which the assessment is required, that are adequate—

"(i) to assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations; and

"(ii) to support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective.

"(B) SIMILAR COURSE OF DISEASE OR SIMILAR EFFECT OF DRUG OR BIOLOGICAL PRODUCT.—

"(i) IN GENERAL.—If the course of the disease and the effects of the drug are sufficiently similar in adults

and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies.

"(ii) EXTRAPOLATION BETWEEN AGE GROUPS.—A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group.

"(3) DEFERRAL.—On the initiative of the Secretary or at the request of the applicant, the Secretary may defer submission of some or all assessments required under paragraph (1) until a specified date after approval of the drug or issuance of the license for a biological product if—

"(A) the Secretary finds that—

"(i) the drug or biological product is ready for approval for use in adults before pediatric studies are complete;

"(ii) pediatric studies should be delayed until additional safety or effectiveness data have been collected; or

"(iii) there is another appropriate reason for deferral; and

"(B) the applicant submits to the Secretary—

"(i) certification of the grounds for deferring the assessments;

"(ii) a description of the planned or ongoing studies; and

"(iii) evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.

"(4) WAIVERS.—

"(A) FULL WAIVER.—On the initiative of the Secretary or at the request of an applicant, the Secretary shall grant a full waiver, as appropriate, of the requirement to submit assessments for a drug or biological product under this subsection if the applicant certifies and the Secretary finds that—

"(i) necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed);

"(ii) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups; or

"(iii) the drug or biological product—

"(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and

"(II) is not likely to be used in a substantial number of pediatric patients.

"(B) PARTIAL WAIVER.—On the initiative of the Secretary or at the request of an applicant, the Secretary shall grant a partial waiver, as appropriate, of the requirement to submit assessments for a drug or biological product under this subsection with respect to a specific pediatric

age group if the applicant certifies and the Secretary finds that—

"(i) necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed);

"(ii) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group;

"(iii) the drug or biological product—

"(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and

"(II) is not likely to be used by a substantial number of pediatric patients in that age group; or

"(iv) the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

"(C) PEDIATRIC FORMULATION NOT POSSIBLE.—If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver shall cover only the pediatric groups requiring that formulation.

"(D) LABELING REQUIREMENT.—If the Secretary grants a full or partial waiver because there is evidence that a drug or biological product would be ineffective or unsafe in pediatric populations, the information shall be included in the labeling for the drug or biological product.

"(b) MARKETED DRUGS AND BIOLOGICAL PRODUCTS.—

"(1) IN GENERAL.—After providing notice in the form of a letter and an opportunity for written response and a meeting, which may include an advisory committee meeting, the Secretary may (by order in the form of a letter) require the holder of an approved application for a drug under section 505 or the holder of a license for a biological product under section 351 of the Public Health Service Act (42 U.S.C. 262) to submit by a specified date the assessments described in subsection (a)(2) if the Secretary finds that—

"(A)(i) the drug or biological product is used for a substantial number of pediatric patients for the labeled indications; and

"(ii) the absence of adequate labeling could pose significant risks to pediatric patients; or

"(B)(i) there is reason to believe that the drug or biological product would represent a meaningful therapeutic benefit over existing therapies for pediatric patients for one or more of the claimed indications; and

"(ii) the absence of adequate labeling could pose significant risks to pediatric patients.

"(2) WAIVERS.—

"(A) FULL WAIVER.—At the request of an applicant, the Secretary shall grant a full waiver, as appropriate, of the requirement to submit assessments under this subsection if the applicant certifies and the Secretary finds that—

"(i) necessary studies are impossible or highly impracticable (because, for example, the number of

patients in that age group is so small or patients in that age group are geographically dispersed); or

"(ii) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups.

"(B) PARTIAL WAIVER.—At the request of an applicant, the Secretary shall grant a partial waiver, as appropriate, of the requirement to submit assessments under this subsection with respect to a specific pediatric age group if the applicant certifies and the Secretary finds that—

"(i) necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed);

"(ii) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group;

"(iii)(I) the drug or biological product—

"(aa) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and

"(bb) is not likely to be used in a substantial number of pediatric patients in that age group; and

"(II) the absence of adequate labeling could not pose significant risks to pediatric patients; or

"(iv) the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

"(C) PEDIATRIC FORMULATION NOT POSSIBLE.—If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver shall cover only the pediatric groups requiring that formulation.

"(D) LABELING REQUIREMENT.—If the Secretary grants a full or partial waiver because there is evidence that a drug or biological product would be ineffective or unsafe in pediatric populations, the information shall be included in the labeling for the drug or biological product.

"(3) RELATIONSHIP TO OTHER PEDIATRIC PROVISIONS.—

"(A) NO ASSESSMENT WITHOUT WRITTEN REQUEST.—No assessment may be required under paragraph (1) for a drug subject to an approved application under section 505 unless—

"(i) the Secretary has issued a written request for a related pediatric study under section 505A(c) of this Act or section 409I of the Public Health Service Act (42 U.S.C. 284m);

"(ii)(I) if the request was made under section 505A(c)—

"(aa) the recipient of the written request does not agree to the request; or

"(bb) the Secretary does not receive a response as specified under section 505A(d)(4)(A); or

"(II) if the request was made under section 409I of the Public Health Service Act (42 U.S.C. 284m)—

"(aa) the recipient of the written request does not agree to the request; or

"(bb) the Secretary does not receive a response as specified under section 409I(c)(2) of that Act; and

"(iii)(I) the Secretary certifies under subparagraph (B) that there are insufficient funds under sections 409I and 499 of the Public Health Service Act (42 U.S.C. 284m, 290b) to conduct the study; or

"(II) the Secretary publishes in the Federal Register a certification that certifies that—

"(aa) no contract or grant has been awarded under section 409I or 499 of the Public Health Service Act (42 U.S.C. 284m, 290b); and

"(bb) not less than 270 days have passed since the date of a certification under subparagraph (B) that there are sufficient funds to conduct the study.

"(B) NO AGREEMENT TO REQUEST.—Not later than 60 days after determining that no holder will agree to the written request (including a determination that the Secretary has not received a response specified under section 505A(d) of this Act or section 409I of the Public Health Service Act (42 U.S.C. 284m), the Secretary shall certify whether the Secretary has sufficient funds to conduct the study under section 409I or 499 of the Public Health Service Act (42 U.S.C. 284m, 290b), taking into account the prioritization under section 409I.

"(c) MEANINGFUL THERAPEUTIC BENEFIT.—For the purposes of paragraph (4)(A)(iii)(I) and (4)(B)(iii)(I) of subsection (a) and paragraphs (1)(B)(i) and (2)(B)(iii)(I)(aa) of subsection (b), a drug or biological product shall be considered to represent a meaningful therapeutic benefit over existing therapies if the Secretary estimates that—

"(1) if approved, the drug or biological product would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared with marketed products adequately labeled for that use in the relevant pediatric population; or

"(2) the drug or biological product is in a class of products or for an indication for which there is a need for additional options.

"(d) SUBMISSION OF ASSESSMENTS.—If a person fails to submit an assessment described in subsection (a)(2), or a request for approval of a pediatric formulation described in subsection (a) or (b), in accordance with applicable provisions of subsections (a) and (b)—

"(1) the drug or biological product that is the subject of the assessment or request may be considered misbranded solely because of that failure and subject to relevant enforcement action (except that the drug or biological product shall not be subject to action under section 303); but

"(2) the failure to submit the assessment or request shall not be the basis for a proceeding—

"(A) to withdraw approval for a drug under section 505(e); or

"(B) to revoke the license for a biological product under section 351 of the Public Health Service Act (42 U.S.C. 262).

"(e) MEETINGS.—Before and during the investigational process for a new drug or biological product, the Secretary shall meet at appropriate times with the sponsor of the new drug or biological product to discuss—

"(1) information that the sponsor submits on plans and timelines for pediatric studies; or

"(2) any planned request by the sponsor for waiver or deferral of pediatric studies.

"(f) SCOPE OF AUTHORITY.—Nothing in this section provides to the Secretary any authority to require a pediatric assessment of any drug or biological product, or any assessment regarding other populations or uses of a drug or biological product, other than the pediatric assessments described in this section.

"(g) ORPHAN DRUGS.—Unless the Secretary requires otherwise by regulation, this section does not apply to any drug for an indication for which orphan designation has been granted under section 526.

"(h) INTEGRATION WITH OTHER PEDIATRIC STUDIES.—The authority under this section shall remain in effect so long as an application subject to this section may be accepted for filing by the Secretary on or before the date specified in section 505A(n).".

(b) CONFORMING AMENDMENTS.—(1) Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)(1)) is amended in the second sentence—

(A) by striking "and (F)" and inserting "(F)"; and

(B) by striking the period at the end and inserting ", and (G) any assessments required under section 505B.".

(2) Section 505A(h) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(h)) is amended—

(A) in the subsection heading, by striking "REGULATIONS" and inserting "PEDIATRIC RESEARCH REQUIREMENTS"; and

(B) by striking "pursuant to regulations promulgated by the Secretary" and inserting "by a provision of law (including a regulation) other than this section".

(3) Section 351(a)(2) of the Public Health Service Act (42 U.S.C. 262(a)(2)) is amended—

(A) by redesignating subparagraph (B) as subparagraph (C); and

(B) by inserting after subparagraph (A) the following:

"(B) PEDIATRIC STUDIES.—A person that submits an application for a license under this paragraph shall submit to the Secretary as part of the application any assessments required under section 505B of the Federal Food, Drug, and Cosmetic Act.".

SEC. 3. TECHNICAL AND CONFORMING AMENDMENTS.

(a) ABBREVIATED NEW DRUG APPLICATION.—Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) is amended in subparagraphs (A) and (B) of subsection (b)(2) and subparagraphs (A) and (B) of subsection (c)(2) by striking "505(j)(4)(B)" and inserting "505(j)(5)(B)".

(b) PEDIATRIC ADVISORY COMMITTEE.—(1) Section 505A(i)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(i)(2)) is amended by striking "Advisory Subcommittee of the Anti-Infective Drugs" each place it appears.

(2) Section 14 of the Best Pharmaceuticals for Children Act (42 U.S.C. 284m note; Public Law 107–109) is amended—

(A) in the section heading, by striking "**PHARMACOLOGY**";

(B) in subsection (a), by striking "(42 U.S.C. 217a)," and inserting (42 U.S.C. 217a) or other appropriate authority,";

(C) in subsection (b)—

(i) in paragraph (1), by striking "and in consultation with the Director of the National Institutes of Health"; and

(ii) in paragraph (2), by striking "and 505A" and inserting "505A, and 505B"; and

(D) by striking "pharmacology" each place it appears and inserting "therapeutics".

(3) Section 15(a)(2)(A) of the Best Pharmaceuticals for Children Act (115 Stat. 1419) is amended by striking "Pharmacology".

(4) Section 16(1)(C) of the Best Pharmaceuticals for Children Act (21 U.S.C. 355a note; Public Law 107–109) is amended by striking "Advisory Subcommittee of the Anti-Infective Drugs".

(5) Section 17(b)(1) of the Best Pharmaceuticals for Children Act (21 U.S.C. 355b(b)(1)) is amended in the second sentence by striking "Advisory Subcommittee of the Anti-Infective Drugs".

(6) Paragraphs (8), (9), and (11) of section 409I(c) of the Public Health Service Act (42 U.S.C. 284m(c)) are amended by striking "Advisory Subcommittee of the Anti-Infective Drugs" each place it appears.

SEC. 4. EFFECTIVE DATE.

(a) IN GENERAL.—Subject to subsection (b), this Act and the amendments made by this Act take effect on the date of enactment of this Act.

(b) APPLICABILITY TO NEW DRUGS AND BIOLOGICAL PRODUCTS.—

(1) IN GENERAL.—Subsection (a) of section 505B of the Federal Food, Drug, and Cosmetic Act (as added by section 2) shall apply to an application described in paragraph (1) of that subsection submitted to the Secretary of Health and Human Services on or after April 1, 1999.

(2) WAIVERS AND DEFERRALS.—

(A) WAIVER OR DEFERRAL GRANTED.—If, with respect to an application submitted to the Secretary of Health and Human Services between April 1, 1999, and the date of enactment of this Act, a waiver or deferral of pediatric assessments was granted under regulations of the Secretary then in effect, the waiver or deferral shall be a waiver or deferral under subsection (a) of section 505B of the Federal Food, Drug, and Cosmetic Act, except that any date specified in such a deferral shall be extended by the number of days that is equal to the number of days between October 17, 2002, and the date of enactment of this Act.

(B) WAIVER AND DEFERRAL NOT GRANTED.—If, with respect to an application submitted to the Secretary of Health and Human Services between April 1, 1999, and the date of enactment of this Act, neither a waiver nor deferral of pediatric assessments was granted under regulations of the Secretary then in effect, the person that submitted the application shall be required to submit assessments under subsection (a)(2) of section 505B of the Federal Food, Drug, and Cosmetic Act on the date that is the later of—

(i) the date that is 1 year after the date of enactment of this Act; or

(ii) such date as the Secretary may specify under subsection (a)(3) of that section;

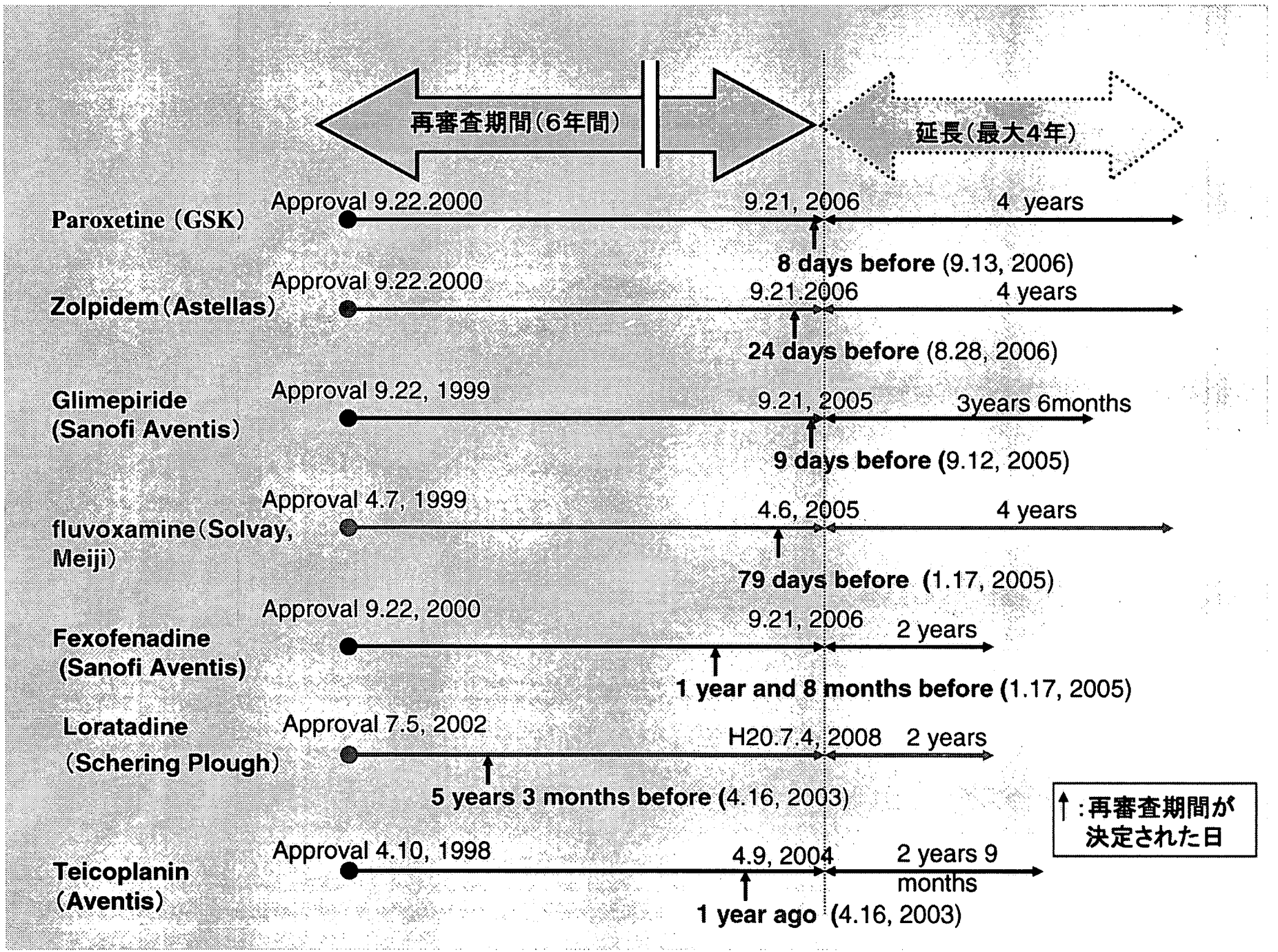
unless the Secretary grants a waiver under subsection (a)(4) of that section.

(c) NO LIMITATION OF AUTHORITY.—Neither the lack of guidance or regulations to implement this Act or the amendments made by this Act nor the pendency of the process for issuing guidance or regulations shall limit the authority of the Secretary of Health and Human Services under, or defer any requirement under, this Act or those amendments.

Speaker of the House of Representatives.

Vice President of the United States and
President of the Senate.

資料３．　我が国の小児医薬品に対する再審査期間の延長のタイミング


再審査期間(6年間)
延長(最大4年)
Paroxetine (GSK)
Approval 9.22.2000
9.21, 2006
4 years
8 days before (9.13, 2006)
Zolpidem (Astellas)
Approval 9.22.2000
9.21.2006
4 years
24 days before (8.28, 2006)
Glimepiride (Sanofi Aventis)
Approval 9.22, 1999
9.21, 2005
3years 6months
9 days before (9.12, 2005)
fluvoxamine (Solvay, Meiji)
Approval 4.7, 1999
4.6, 2005
4 years
79 days before (1.17, 2005)
Fexofenadine (Sanofi Aventis)
Approval 9.22, 2000
9.21, 2006
2 years
1 year and 8 months before (1.17, 2005)
Loratadine (Schering Plough)
Approval 7.5, 2002
H20.7.4, 2008
2 years
5 years 3 months before (4.16, 2003)
Teicoplanin (Aventis)
Approval 4.10, 1998
4.9, 2004
2 years 9 months
1 year ago (4.16, 2003)
↑:再審査期間が決定された日

厚生労働科学研究費補助金（医薬品・医療機器等レギュラトリーサイエンス総合事業研究事業）
分担研究報告書

「欧州の小児規制と製薬企業の対応状況に関する調査」

分担研究者　岩崎利信[1,2]，嶌村俊朗[1,3]
日本製薬工業協会医薬品評価委員会臨床評価部会[1]
塩野義製薬（株）[2]，田辺三菱製薬（株）[3]

研究要旨

EU小児規制および当規制の施行に伴う欧州製薬企業の対応状況を調査した。

2007年1月，EUは「Better Medicine for Children」として，小児用医薬品の開発を促進するための規制を施行した。規則の特徴は大きく分け以下の4点である。

① 小児への使用が想定される医薬品については，小児を対象とした臨床試験の実施を原則とする。

② EMEA（欧州医薬品庁）に小児用医薬品の評価を扱うPaediatric Committee(PDCO)を新たに設置する。

③ 小児用医薬品の開発を促進するため製薬企業に経済的インセンティブを付与する。

④ 小児に精通した専門家から構成される小児臨床試験ネットワーク構築を支援する。

小児治験の実施については，PIP(Paediatric Investigation Plan：小児用医薬品開発計画書）を成人治験のPH1終了後に提出することとなっている。成人を対象とした開発の初期段階では，小児治験を計画する際に参考となる情報は非常に少ないため，試験デザインを含む具体的な開発計画の立案は困難である。したがって，最初のPIPには，対象とする疾患など概念的な内容を盛り込むことでよいとの規制当局の見解である。その後，成人の治験データが集積されるに伴い，PIPを具体化していくこととなる。PIPに関する評価は，専門知識も必要となることから新たに設置されたPDCOが担うこととなる。小児疾患や小児治験に精通した専門家を擁するPDCOは，小児の特殊性や実施可能性を踏まえた合理的な開発計画を助言できる。また，ネットワークの整備をEUがサポートし小児治験推進を図ることとしている。さらに，科学的観点からの小児治験推進策だけではなく，市場保護期間の延長やScientific Advice（当局との治験相談）の無料化など経済的インセンティブの付与を規制の中で認めている。これらインセンティブは，小児の治験を実施した医薬品に付与されるものであり，小児効能の承認取得が条件となってはいない。小児治験の義務化を規制により課す一方で，企業の開発動機を高めるインセンティブを盛り込んだEU規制は，国内の小児治験推進策を検討する上で参考とすべきシステムである。

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A. 研究目的

小児への薬物投与の8割は，効能や用法用量が未承認のまま使用される，いわゆる「適応外使用」の状況にある。適応外使用の問題は，医薬品のエビデンス評価が不十分なまま薬物治療が施されていることであり，それを解決するには，臨床試験を実施し，有効性，安全性を担保する適切な用法用量を設定しなければならない。適応外使用の問題については，欧米諸国においても同様の状況であったため，小児治験推進を目的にICH（医薬品開発の国際調和会議）にて小児ガイダン

スが2000年に作成された。

このICHガイダンスの公表を機に，各国とも小児治験を推進するための議論が本格化した。米国では，小児治験の義務化と企業へのインセンティブを包含した規則を施行し，現在まで約140の小児治験が実施され，成果を挙げている。またEUにおいては，2007年，「Better Medicines for Children」を目的に，小児用医薬品の開発推進策が制度化された。

一方，国内では，2005年に適応外使用の問題解決に向けた「小児薬物療法根拠情報収集事業」が発足し，また「有効で安全な医薬品を迅速に提供する検討会報告書」の中でも，医薬品開発に資するインセンティブや保健衛生上の方策も含め小児用医薬品の開発推進が謳われている。このように，小児用医薬品開発の必要性については十分浸透しており，事実，産官学で様々な検討は進んでいるものの，欧米のように制度化されるまでには至っていない。

そこで，日本製薬工業協会医薬品評価委員会臨床評価部会小児グループでは，小児用医薬品の開発推進について，より実効性の高い方策を検討するために，小児治験をテーマにしたEFGCP会議に参加しEUの小児規制を調査することとした。またEFPIA(European Federation of Pharmaceutical Industries' Association：欧州製薬団体連合会)，PhRMA(Pharmaceutical Research and Manufactures of America：米国研究製薬工業協会)の小児グループとの会議を開催し，日本の状況を説明すると共に，欧米企業の具体的な対応についての情報を入手した。さらに，日本を含む国際規模での小児用医薬品開発を視野に入れ，今後3団体が協調して取り組むべき問題について検討した。

B. 調査対象

規制：Regulation(EC) No1901/2006 of The European Parliament and of the Council of12December 2006（資料1）
(http://www.emea.europa.eu/htms/human/paediatrics/introduction.htm)

また関連情報は，下記の学会および会議に参加し入手した。

- The EFGCP Children's Medicines Working Party 3rd Annual Conference(2006 Oct 8-9 in Brussels)
  EFGCPは，臨床研究に関連する様々な領域について，戦略的な対話を助成するフォーラムであり，Children's Medicines Working Partyは，大学の小児科医，規制当局，患者支持団体及び製薬企業団体から構成される。2005年、2006年に続く，3回目の年会議である。
- JPMA/EFPIA/PhRMA Joint Meeting（2006 Oct. 10 at EFPIA Office in Brussels
  ※JPMA：Japan Pharmaceutical Manufacturing Association（日本製薬工業協会）
  JPMA, EFPIA, PhRMAは，各々日本，欧州，米国の開発志向製薬企業から構成される団体である。

C. 調査結果

Ⅰ：EUの小児規制について

1. 経緯

- 1997年
  EUにおいては，1997年よりEMEA(European Medicines Agency：欧州医薬品庁）を中心に小児用医薬品開発についての検討が開始された。小児の臨床試験を推進するためは，制度の強化が必要であるとの見解が出され，特にインセンティブのあり方が重要な論点の一つとして取り扱われた。
- 1998年
  小児を対象とした臨床試験の推進については，国際的な取り組みが必要との認識から，ICHで議論したいとの要望がEU規制当局から出された。この要望を受け，ICH 有効性分野の11番目のトピックとして，小児臨床試験が採択され，EUでは2002年6月にガイダンスとして通知された。また関連して，2006年 EC(European Commission)は，' Ethical consideration for clinical trials performed in children'の草案を公表している。
- 2002年
  ECは「'Better Medicines for children-proposed regulatory actions in paediatric medical product'」と

して，小児治験推進のための規制化を提案した。この小児規制の案に対しては，経済的・社会的影響や他の規制への影響など更なる評価が必要との見解が外部から寄せられ，引き続き，法制化の必要性について包括的な評価がなされることになった。最終的には小児臨床試験の推進を目的とした法制化が認められ，2004年から具体的な作成作業に入った。

・ 2004年

小児用医薬品に関する規制初案が議会に提出された。

2006年

EU議会は，当規制の制定に合意した。

この規制は，2007年1月26日から施行されることになった。

Regulation (EC) No1901/2006, amending Regulation(EC) No1902/2006

2. 小児規制の骨子

Regulation (EC) No1901/2006の骨子は以下のとおりである。

1) EMEA内に，専門家から構成される小児委員会(Paediatric Committee :PDCO)を設置する。
2) 企業は，PIP (Paediatric Investigation Plan:小児用医薬品開発計画書) を，医薬品開発の初期に提出すること。
3) PIPは後発品もしくはこれに類似する医薬品(Biosimilar, Herbal, Homeopathic品等)には適用されない。
4) 合理的な理由により早期に小児治験を開始することが望ましくない場合は，開始時期の延期(Deferral)を認める。
5) 合理的な理由により，小児を対象とした臨床試験の実施が望ましくない場合は，試験実施を免除する (Waiver)。
6) 小児臨床試験に関するScientific Advice(治験相談)は無料とする。
7) 小児臨床試験に関する情報 (試験結果，PIP，免除および延期に関する記録) を製品情報に含むこと。
8) 特許が失効した医薬品については，PUMA(Paediatric Use Marketing Authorization)を新たに設定し，小児のデータを対象に8-10年の保護期間を与える。
9) 特許権を有する医薬品については，SPC(Supplementary Protection certification)に6ヶ月間の延長を認める。
10) 稀少疾病医薬品の指定を受けた医薬品については，10年間の先発権を12年間まで延長する。
11) PIPに従い実施した臨床試験の成績は，試験の完了・未完を問わず，EUにおいて試験の登録をすべきである。
12) 小児における臨床試験には，専門的な知識が必要とされる場合もあるため，ネットワークの構築を推進する。

3. Paediatric Committee(PDCO)について

1) 役割

・ PIPの評価
・ PIPに従い実施された小児治験の結果の評価
ただし，PDCOは，小児用医薬品開発に係わる科学的評価は行うが，承認の可否を判断する権限は有していない。
・ 既存薬で適応外として小児に使用されている医薬品について，集積すべきデータを規制当局へ助言する。
・ 小児治験ネットワーク構築のための助言
・ 小児への適用が必要な医薬品リストの作成および見直し
・ 会議は月に1回開催される

2) 構成

・ CHMP (Committee for Medicinal Products for Human Use)メンバー 5名
・ 各加盟国からの委員 22名
・ 医学専門家 (Health Professionals) 3名
・ 患者団体代表 3名

3) 現在の活動状況

・ 組織体制の整備
・ PIP/WaiverのSmReportに関する様式の検討
・ EMEA Committee, CHMPとの調整

4. PIPについて

1） 様式

PIP を含む小児臨床試験の申請に係わる申請様式および内容は以下のパートA～Fで構成される。PIP に関しては，Part D に記載されている。

- **Part A**: Administrative and Format
- **Part B**: Overall development of the medicinal product including information on the target diseases/conditions
- **Part C** : Applications for product specific waivers
- **Part D**: Paediatric Investigation Plan(PIP)

D1: Overall Strategy Proposed by Applicant for the Paediatric Development

1. 対象とする疾患
2. 対象とする年齢と年齢区分
3. 品質，非臨床/臨床データの骨子
   成人での臨床試験の骨子をIB（治験薬概要書）形式で提出する。また非臨床データ/臨床データも必要であれば提示する。
4. 成人と小児間の外挿可能性についての評価
5. 既に入手している小児関連情報
   文献，適用外で使用されている場合には関連情報，クラスエフェクトとして認識されている突発的な薬物暴露情報
6. 治療上の便益
   以下の事項が明らかな場合，「便益を有する」と考えられる。

a) 既存の治療に比べ有効性で優っている
b) 既存の治療と比べ安全性の面で改善が見られる
c) 有効性，安全性，服用性の改善が期待できる新たな用法用量や投与経路の設定
d) 年齢群に応じた新規製剤の開発
e) 新たな臨床的知見や情報を提供できる
f) 有効性や安全性の改善が期待できる新たな作用機序を有する

D2 : Strategy in Relation to Quality Aspects

投与方法に関する科学的・薬学的・薬理学的特性を記載する。具体的には

- 特定の年齢群を対象とした新規製剤の必要性
- 製剤開発のための開発スケジュール
- 添加剤などの情報
- 投与方法に関連する情報（特殊な機器の使用，食物との配合性，容器について）

D3 : Strategy in Relation to Non-clinical Aspects

既存の非臨床データに加え，幼若動物等を用いた薬理学的情報，薬物動態情報，毒性情報を記載する。

D4 : Strategy in Relation to Clinical Aspects

既存の医薬品開発から得られる情報に加え，小児の特性に配慮した開発戦略の概要を述べる。

- 成人と小児間の薬物動態/薬力学の差異
- 必要な臨床データ
  用量反応試験の必要性，年齢区分に応じた試験計画の必要性，試験に用いる評価指標の妥当性やサロゲートマーカーの必要性，市販後臨床試験や長期試験の必要性など。

D5 : Planned Measures for the Paediatric Development

D.5.1 非臨床試験成績一覧の概要

D.5.2 計画している各試験の概要

D.5.3 計画あるいは完了した非臨床試験計画書のシノプシス/概要

- 試験のタイプ，目的，試験に用いた動物種，投与方法，投与期間

D.5.4 計画あるいは完了した臨床試験計画書のシノプシス/概要

- 試験デザイン
- 対照群（プラセボ，実薬）
- 試験実施地域
- 治験薬の用法用量，投与経路
- 試験の目的
- 被験者数（男女比率），年齢，ICH小児ガイダンスに従った年齢区分毎の被験者数

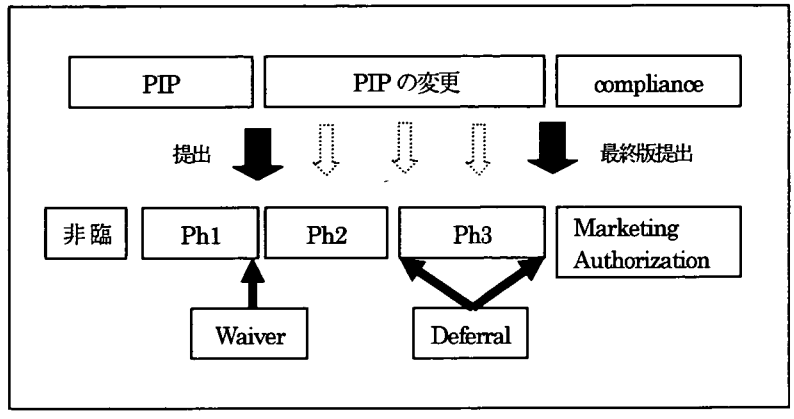
・治療期間
・選択/除外基準
・主要（副次）評価項目
・サンプルサイズ
・検出力（エフェクトサイズ）
・被験者の組み込み，中間解析，Stopping Rule
・解析方法

D.6 PIPのスケジュール

ICH 小児ガイダンスに記載されている試験開始の時期の考えに従い，詳細な試験計画のスケジュールを記載する。

プロセスをとることになる。（下図参照）

ただし，PIPは早期に提出しなければならないが，試験の実施時期については，必ずしも早期の開始を求めるものではない。



・Part E:Applications for Deferrals

小児臨床試験の開始を遅らせることが可能かどうかは，対象疾患，投与経路，製剤から判断されるべきである。例えば，安全性等の懸念から成人の治験が完了した後に実施することが適切な場合，成人より試験期間が長くなる場合，非臨床データの追加が必要な場合など。

・小児臨床試験は必要であるが，そのために成人の治験が遅れるようなことがあってはならない。

・Part F:Modification of an Agreed Paediatric Investigation Plan

2）PIPの手順

PIPは成人のPH1終了後に提出する。PIPに記載する情報は上記に記したとおりである。

成人のPH1終了時点では，PIPに記載すべき情報は非常に少ないため，具体性のある試験計画書は作成できない。実際，今回の学会等でも，PIPには何を記載すべきかについての質問が当局に多く寄せられていた。これに対しEMEAは「小児用医薬品の開発コンセプト」を記載すればよいとの回答であった。この時点で具体的に記載すべき情報は定義づけられていないが，薬剤が小児にも使用されるかどうかなど，まずは開発の意志表示をするということである。その後，成人の治験データの集積に従い，PIPを修正していき完成させるという

5. インセンティブについて

EU規制では，新薬および特許切れの医薬品について，市場独占期間の延長等を認め，小児治験推進に資するインセンティブを認めている。

・小児治験を実施した新薬

SPC（Supplementary Protection Certification）で認められているデータ保護期間を6ヶ月延長する。この延長は，有効成分を対象とするため成人用製剤にも適用される。

・小児治験を実施した特許が失効している医薬品については，PUMA（Paediatric Use Marketing Authorization）を新たに設置し，小児データを8-10年保護する。つまり，後発品は，成人を対象とした承認申請は可能であるが，小児の効能は保護期間中は取得できないことになる。（添付資料：off patent drug list）

・オーファン医薬品

・通常10年の保護期間を12年に延長する。

EU議会でも，新薬の市場保護期間を延長するインセンティブの付与については，後発品の参入を妨げ，医療費の増加につながるとの批判があった。これに対し小児委員会は，1試験あたりの開発費用を相殺するために必要な保護期間は6ヶ月であること，後発品の参入が遅れることで後発品メーカーが受ける損失は1品目あたり€800,000～€900,000であり，EUにおける薬剤費の上昇率は0.06～0.25%であると推定した（RAND

Study)。後発品参入を遅らせることで生じる薬剤費の上昇率は僅かであり，インセンティブを付与することで小児治験が拡大し，その結果，適切な薬物療法を小児に施せるメリットを考えれば，インセンティブを規制の中に認めることは妥当であるとの結論に至った。

6. 小児治験推進のための基盤整備

小児治験の推進には，実際に治験を実施する施設やネットワークの体制整備が必要である。そこで MICE (Medicine Investigation for the Children of Europe)が設置され，治験推進のための資金提供を行うとしている。また，臨床研究情報の提供や小児保護の観点から研究グループ間で類似した試験の重複を避けるため，治験の実施状況を公開することを意図した「小児治験の登録」を EU 小児規制で義務化した。

また，海外データ（FDA）からの受け入れにも積極的に取り組もうとしている。

Ⅱ．EU 規制に対する製薬企業の取り組み状況

- The EFGCP Children's Medicines Working Party 3rd Annual Conference (2006 Oct 8-9 in Brussels)
- JPMA/EFPIA/PhRMA Joint Meeting (2006 Oct. 10 at EFPIA Office in Brussels)

上記の学会，会議に参加し，各企業の対応状況についての調査および情報交換を行った。

1. PIP について

・PIP を PH1 後に提出することになるが，この時点では，具体的な開発計画書は提示できない。「コンセプト」の記載でよいとのことであるが，どのような記載内容とするかは明らかではなく，個別に対応していくことになる。

・PIP は，成人データの集積に伴い，修正をかけていくことになるが，製薬企業としては FDA の規制要件も考慮しなければならない。米国でも小児治験を義務化しており，実施すべき試験を記載した「Written Request」が成人の Ph2 以降に FDA から企業へ送付される。EMEA と早い段階から検討している PIP の内容と FDA から要求される試験内容が異なれば，別々の小児治験を実施する状況となる。試験の重複を避けるためにも，実施すべき必要な試験については，EMEA と FDA の間で調和を図るよう企業として要求している。

これについては，FDA と EMEA とで，月に 1 回小児治験についての会議を開催している。できる限り 1 つの試験で両当局の要件を満たせるように配慮するとの EMEA のコメントであった。

2. インセンティブについて

・米国も小児治験を実施した場合，6 ヶ月の先発期間の延長を規制にて認めている。2007 年の法改正では，ブロックバスター（年間売り上げ 10 億ドル以上）については，対象外とすることになった。欧米とも先発権延長によるメリットについては，当該製品の市場の大きさによるため，すべての医薬品が小児治験に要する開発費用を相殺できるということはない。総合的に見て，どの程度のメリットになるかは，今後，評価していくことになる。

3. 製剤開発について

EU 内でも国により，好まれる小児剤型は異なっている。治験段階で，商用製剤を用いることは時間的にも経済的にも負担が大きいので，治験薬を溶解したり，懸濁させたものを治験で使用している。その治験薬と各国の嗜好にあわせた商用製剤の同等性を確認することで上市が認められる。

4. 非臨床試験の必要性について

幼若動物を用いた毒性試験等は，必ずしも実施する必要はない。米国，EU とも同じ状況である。日本においても，必ずしも実施しなければならないとの規制要件は出されていないが，殆どの場合，小児治験開始前に実施するのが慣習化している。幼若動物試験が必要な場合など，例えば ICH E3 ガイダンス（医薬品の臨床試験のための非臨床安全性試験の実施時期について）で詰めることを提案してはどうかとの意見が出された。