- Encouraging transparency of information on products and treatments currently used in children through the establishment of a database, and including also information where studies have resulted in contraindications or other restrictions to use in children.

- Facilitating international collaboration and exchange of regulatory information.

**2. Ensuring that pharmacovigilance mechanisms are adapted** to meet the challenges of possible long-term effects in specific cases

Consideration of whether there is a need to develop specific post-authorisation obligations for specific medicinal products to be used in children.

**3. Facilitating the avoidance of unnecessary studies** through the publication of details of clinical trials already initiated and better exchange of information.

**4. Establishment of a list of priorities for research** on existing authorised medicinal products in accordance with public health needs and which may include priorities in **different therapeutic classes.**

**5. Developing European excellence in the field of research, development and assessment of clinical trials** for paediatric medicinal products, through the creation of a specific and dedicated committee or expert group within the European Medicines Evaluation Agency (EMEA) and through promoting the creation of a European paediatric network for performing paediatric studies.

6. Ensuring that the **highest ethical criteria** are met, as laid down in the specific provisions for the protection of children in the recently adopted **Directive 2001/20/EC on Good Clinical Practice** and as described above.

## IV. AVENUES TO EXPLORE OR PROPOSED MEANS OF ACHIEVING THESE OBJECTIVES

It is suggested that a new set of legislative provisions may be necessary to achieve the objectives outlined. At the November 2001 Brainstorming meeting of Member States, held within the framework of the Commission's Pharmaceutical Committee, the importance of taking a European wide approach was stressed, taken into account single market considerations and development efficiencies.

### 1. Incentives for research

In the EU, as in the US, it is clear that market forces are inadequate to stimulate the necessary studies in children. A system of Community incentives is necessary both to encourage appropriate studies on products already on the market and to ensure that new applications for marketing authorisations will include the necessary studies to ensure they are adapted to the needs of children of different age groups.

A number of possible incentive mechanisms could be considered. These are not mutually exclusive:

*Encouraging the performance of appropriate studies for medicinal products for which protection of intellectual property exists*

It is proposed to introduce an additional period of market exclusivity as a reward for submitting one or more validated clinical studies on children of one or more age groups.

This period of market exclusivity would apply at the end of the existing period of patent or Supplementary Protection Certificate (SPC) protection. Regulatory authorities would be required not to accept applications for generic marketing authorisations until this additional period had elapsed. A mechanism similar to the "written request" system in the US could be developed in order to ensure that the studies performed were both useful and appropriate. One possibility would be to ask companies to submit a development plan, which would be assessed by an EU expert group before agreeing eligibility for the clinical studies to be considered within the new legal provisions. A mechanism to pre-define criteria in order to avoid unnecessary studies could also be put in place.

*Encouraging the performance of appropriate studies for already marketed medicinal products for which no intellectual property exists*

a) Introduction of a period of data protection for a marketing authorisation with a paediatric indication (in a similar way to the exclusivity provided to the orphan indication in the EU regulation for orphan medicinal products) through the creation of a new type of "kid" marketing authorisation.

The protection would be valid for the active substance/indication combination. In order to help this to work in practice, it would be possible to create a new kind of marketing authorisation, possibly with a specific prefix or suffix, e.g. "Kid – XYZ (drug)" or "Paed-drug". This would facilitate the distinction with an existing marketing authorisation and would help to ensure that the new paediatric data was protected and thus a valuable commodity. It would be applicable for medicinal products where no intellectual property right existed. In addition it would allow companies who were not the originator to exploit known medicinal products and develop specific formulations supported by specific studies.

Only the paediatric indication would benefit from the data protection provisions.

b) Creation of a fund which could be used to fund clinical or non-clinical paediatric research. Current estimates from the US National Institute of Health indicate that a safety and efficacy study may cost between $1 and $7.5 million, depending on the number of children participating and the type of medicinal product being studied. Industry sources quote higher estimates from $5 to $35 million. For the 400 studies started in the US between 1997 and 2001, this represents an annual budgetary requirement of approximately $670 million. The new recently adopted US act allocates $200 million annually. In Europe, based on an average estimate of €5 million per trial, 20 studies could be performed annually at a cost of about €100 million.

Despite the variance in these estimates, it is clear that a significant source of income is required in an area where there is little other incentive to do this work and that a source of income to finance these studies must be found. One possibility would be to use some of the proceeds from the additional profits made by the extension of the intellectual property or market exclusivity provisions to create a fund, which could then be used for further studies on already marketed products. In principle, this fund could then be used to contract out certain research projects.

c) Investigation of existing national and community sources of research funding.

In the provisions of the chapter on *Strengthening the Foundations of the European Research Area*, in the text of the sixth framework programme, specific mention of efforts

to co-ordinate research activities in the area of health, including health issues in children is made. Additionally there may be a possibility to support clinical trials in children in the area of cancer research or in other areas such as diabetes, and rare diseases provided that the trials incorporate some aspects of "genomic" research in one way or another.

Investigation of research funding at national level - certain limited funding has already been sought at national level for similar initiatives in some Member States, notably UK and Germany. For example, in Germany there is a possibility of funding from the Federal Ministry of Education and Research (BMBF) sufficient to cover one or two studies annually.

**2. New applications for marketing authorisations – legal requirement for clinical trials in children**

It is suggested that an approach similar to that adopted in the context of the US paediatric rule be taken, that is to routinely require studies in paediatric populations as part of the marketing authorisation application requirements. Applicants would be required to submit the results of studies performed as a requirement for validation. Paediatric applications would be screened by a European expert group, which would determine whether or not the studies were acceptable in principle (e.g. corresponding to pre-defined criteria) The assessment of the studies would then form part of the normal assessment of the marketing authorisation. The possibility of a waiver would be necessary in certain justified cases where there is no therapeutic need in paediatric populations (e.g. Alzheimer's disease, certain heart conditions). It would be the responsibility of the applicant to justify the need for a waiver. In certain cases it may be possible to defer the completion of the studies until after the application for the adult population had been submitted, on the basis of a development plan and justification provided by the applicant.

In any event, compliance with Directive 2001/20/EC on clinical trials and with ethical principles will be assured.

**3. Transparency- creation of a central database**

*a) Existing data on medicinal products (including off-label use in children)*

Although published data indicates that most of medicinal products used to treat paediatric populations have never been studied in the target population, in fact there is a certain amount of published (often poorly documented) experience with the use of certain medicinal products in children, particularly in the area of intensive care and specialist treatments. An attempt to collect this information would be useful in order to determine priorities for future work and/or to ensure that the same information and treatment possibilities were available throughout the EU.

It should be noted that, although they may not have official endorsement, "paediatric formularies" have already been put together in several countries such as the British Formulary on Medicines for Children in the UK and the "Vidal pédiatrique" in France.

It is suggested that a central database to ensure that this information is collected and made available should be set up.

Information on all new approved indications and on the outcomes of negative trials should also be collected and made publicly available.

*b) Use of the database foreseen by Directive 2001/20/EC for information on clinical trials*

In order to avoid the possible repetition of studies in children which do not add to the collective knowledge, the scope and application of the European database foreseen in Article 11 of Directive 2001/20 should be examined in the specific context of clinical trials in children. A method to avoid this type of repetition, prior to their commencement, should be developed.

**4. Developing European excellence –establishment of an EU scientific expert group**

One of the advantages that the US has over the EU in the area of clinical trial development is the fact that there is regulatory oversight through the "IND" Investigational New Drug application from an early stage of product development. This contributes also to the development and maintenance of specific regulatory expertise. Although the traditional EU approach has been less interventional when it comes to the design of clinical trials, the growth of the "scientific advice" facility in the EU marketing authorisation application process and the requests for protocol assistance in the context of the development of orphan medicinal products shows clearly that there is growing support for EU regulatory intervention at an early stage of the product development.

It is proposed to create an EU expert group or working party within the European Medicines Evaluation Agency (EMEA) with specific responsibility for all aspects relating to the development, availability and follow up of paediatric medicines.

**5. Encouraging submission of trials in Europe that have been accepted internationally**

The US paediatric exclusivity provision has to-date (January 2002) encouraged over 400 specific studies to be performed, resulting in a large amount of information on paediatric use and 21 labelling changes. So far there is little evidence that these studies have been submitted for regulatory approval in the EU and/or to support labelling changes in medicinal products that have been authorised in the EU.

If a clinical study has been performed according to internationally accepted GCP standards and in accordance with the internationally accepted guidelines on medicinal products in children (ICH E11) then it would be expected that this clinical study would be accepted with minimal additional requests for information. If acceptable and robust studies have been performed, then it cannot be ethically justified either to repeat these studies or to require significant additional data.

Ideally any studies that have already been performed outside of the EU should be used to introduce useful information, in particular to support or to contraindicate paediatric indications in medicinal products that are on the EU market. This depends on the studies being submitted as part of a marketing authorisation, variation, or extension application to an EU regulatory authority. It is therefore important to have a mechanism to ensure that these studies will actually be submitted as part of an application for authorisation in the EU and assessed in a harmonised manner.

**6. Post-authorisation issues – possible need for long term follow-up**

Although the requirement to report adverse reactions on medicinal products used in treatments applies in the same way as for adult medicines, the fact that there is such a large percentage of unauthorised or "off-label" use implies that the extent of adverse reactions actually reported may be significantly less than those encountered in medical practice. This, combined with the small size of many treated paediatric populations raises the question as to whether a system of spontaneous adverse reaction reporting is the only appropriate mechanism to properly manage the risk of medicinal products used in children. The possibility of requiring more dedicated follow-up pharmacovigilance studies for certain high-risk products could be considered. Cases where a specific adverse reaction is anticipated, specific studies to monitor these reactions could be requested.

An additional concern with respect to the effect of medicinal products used in young children on their future development and maturity exists. As with all medicines there is a careful balance between benefits and risks to be achieved. However in order for this to be properly assessed in the case of medicines to treat children, there may be a need, in specific cases to include a provision to monitor treated children for a longer term and in some cases throughout their entire lives. This type of exercise would inevitably be both difficult and costly for companies to perform.

### 7. Creation of a Pan-European network of clinical excellence for performance of paediatric studies

Clinical trials in children may require specific expertise, specific methodology and in some cases, specific facilities. One of the challenges of creating a system which will effectively increase the number of clinical trials performed to develop or adapt medicines for use in children is the need to ensure that these studies are carried out in suitably adapted facilities by appropriately trained investigators and paediatricians. A number of initiatives to create networks of paediatricians have been taken at national level in Europe, for example initiatives in France, Germany and United Kingdom, but there has been little attempt at cross border collaboration. Consideration should be given to the creation of a Pan-European network which would link together existing national initiatives in order to build up the necessary competences at a European level and to facilitate co-operation and avoid duplication.

## V. Conclusion

Similar measures to those already taken in the US are urgently needed for European children. These must take account of the specificities and structure of the Community market and pharmaceutical regulatory system. Achieving the right combination of incentives and regulatory obligations which will ensure that both existing and new medicinal products are suitably adapted for the needs of paediatric populations in the Community in a resource efficient manner is a challenge that must be met in order to ensure the best and safest treatments for our children. The aim of this paper is to outline potential options of addressing this challenge by new pharmaceutical legislation.

**********

Feedback and comments from all interested parties are invited before the **30th April 2002** at the following address:

- European Commission
  DG ENTERPRISE
  Unit F/2 – Paediatric initiative
  To the attention of Emer Cooke
  Rue d'Arlon 88, 1/56
  B – 1049 – Brussels

S. 1789

# One Hundred Seventh Congress of the United States of America

AT THE FIRST SESSION

*Begun and held at the City of Washington on Wednesday, the third day of January, two thousand and one*

## An Act

To amend the Federal Food, Drug, and Cosmetic Act to improve the safety and efficacy of pharmaceuticals for children.

*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 "Best Pharmaceuticals for Children Act".

**SEC. 2. PEDIATRIC STUDIES OF ALREADY-MARKETED DRUGS.**

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

(1) by striking subsection (b); and

(2) in subsection (c)—

(A) by inserting after "the Secretary" the following: "determines that information relating to the use of an approved drug in the pediatric population may produce health benefits in that population and"; and

(B) by striking "concerning a drug identified in the list described in subsection (b)".

**SEC. 3. RESEARCH FUND FOR THE STUDY OF DRUGS.**

Part B of title IV of the Public Health Service Act (42 U.S.C. 284 et seq.) is amended—

(1) by redesignating the second section 409C, relating to clinical research (42 U.S.C. 284k), as section 409G;

(2) by redesignating the second section 409D, relating to enhancement awards (42 U.S.C. 284l), as section 409H; and

(3) by adding at the end the following:

**"SEC. 409I. PROGRAM FOR PEDIATRIC STUDIES OF DRUGS.**

"(a) LIST OF DRUGS FOR WHICH PEDIATRIC STUDIES ARE NEEDED.—

"(1) IN GENERAL.—Not later than one year after the date of enactment of this section, the Secretary, acting through the Director of the National Institutes of Health and in consultation with the Commissioner of Food and Drugs and experts in pediatric research, shall develop, prioritize, and publish an annual list of approved drugs for which—

"(A)(i) there is an approved application under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j));

"(ii) there is a submitted application that could be approved under the criteria of section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j));

"(iii) there is no patent protection or market exclusivity protection under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.); or

"(iv) there is a referral for inclusion on the list under section 505A(d)(4)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(d)(4)(C)); and

"(B) in the case of a drug referred to in clause (i), (ii), or (iii) of subparagraph (A), additional studies are needed to assess the safety and effectiveness of the use of the drug in the pediatric population.

"(2) CONSIDERATION OF AVAILABLE INFORMATION.—In developing and prioritizing the list under paragraph (1), the Secretary shall consider, for each drug on the list—

"(A) the availability of information concerning the safe and effective use of the drug in the pediatric population;

"(B) whether additional information is needed;

"(C) whether new pediatric studies concerning the drug may produce health benefits in the pediatric population; and

"(D) whether reformulation of the drug is necessary.

"(b) CONTRACTS FOR PEDIATRIC STUDIES.—The Secretary shall award contracts to entities that have the expertise to conduct pediatric clinical trials (including qualified universities, hospitals, laboratories, contract research organizations, federally funded programs such as pediatric pharmacology research units, other public or private institutions, or individuals) to enable the entities to conduct pediatric studies concerning one or more drugs identified in the list described in subsection (a).

"(c) PROCESS FOR CONTRACTS AND LABELING CHANGES.—

"(1) WRITTEN REQUEST TO HOLDERS OF APPROVED APPLICATIONS FOR DRUGS LACKING EXCLUSIVITY.—The Commissioner of Food and Drugs, in consultation with the Director of the National Institutes of Health, may issue a written request (which shall include a timeframe for negotiations for an agreement) for pediatric studies concerning a drug identified in the list described in subsection (a)(1)(A) (except clause (iv)) to all holders of an approved application for the drug under section 505 of the Federal Food, Drug, and Cosmetic Act. Such a written request shall be made in a manner equivalent to the manner in which a written request is made under subsection (a) or (b) of section 505A of the Federal Food, Drug, and Cosmetic Act, including with respect to information provided on the pediatric studies to be conducted pursuant to the request.

"(2) REQUESTS FOR CONTRACT PROPOSALS.—If the Commissioner of Food and Drugs does not receive a response to a written request issued under paragraph (1) within 30 days of the date on which a request was issued, or if a referral described in subsection (a)(1)(A)(iv) is made, the Secretary, acting through the Director of the National Institutes of Health and in consultation with the Commissioner of Food and Drugs, shall publish a request for contract proposals to conduct the pediatric studies described in the written request.

"(3) DISQUALIFICATION.—A holder that receives a first right of refusal shall not be entitled to respond to a request for contract proposals under paragraph (2).

"(4) GUIDANCE.—Not later than 270 days after the date of enactment of this section, the Commissioner of Food and

Drugs shall promulgate guidance to establish the process for the submission of responses to written requests under paragraph (1).

"(5) CONTRACTS.—A contract under this section may be awarded only if a proposal for the contract is submitted to the Secretary in such form and manner, and containing such agreements, assurances, and information as the Secretary determines to be necessary to carry out this section.

"(6) REPORTING OF STUDIES.—

"(A) IN GENERAL.—On completion of a pediatric study in accordance with a contract awarded under this section, a report concerning the study shall be submitted to the Director of the National Institutes of Health and the Commissioner of Food and Drugs. The report shall include all data generated in connection with the study.

"(B) AVAILABILITY OF REPORTS.—Each report submitted under subparagraph (A) shall be considered to be in the public domain (subject to section 505A(d)(4)(D) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(d)(4)(D)) and shall be assigned a docket number by the Commissioner of Food and Drugs. An interested person may submit written comments concerning such pediatric studies to the Commissioner of Food and Drugs, and the written comments shall become part of the docket file with respect to each of the drugs.

"(C) ACTION BY COMMISSIONER.—The Commissioner of Food and Drugs shall take appropriate action in response to the reports submitted under subparagraph (A) in accordance with paragraph (7).

"(7) REQUESTS FOR LABELING CHANGE.—During the 180-day period after the date on which a report is submitted under paragraph (6)(A), the Commissioner of Food and Drugs shall—

"(A) review the report and such other data as are available concerning the safe and effective use in the pediatric population of the drug studied;

"(B) negotiate with the holders of approved applications for the drug studied for any labeling changes that the Commissioner of Food and Drugs determines to be appropriate and requests the holders to make; and

"(C)(i) place in the public docket file a copy of the report and of any requested labeling changes; and

"(ii) publish in the Federal Register a summary of the report and a copy of any requested labeling changes.

"(8) DISPUTE RESOLUTION.—

"(A) REFERRAL TO PEDIATRIC ADVISORY SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE.—If, not later than the end of the 180-day period specified in paragraph (7), the holder of an approved application for the drug involved does not agree to any labeling change requested by the Commissioner of Food and Drugs under that paragraph, the Commissioner of Food and Drugs shall refer the request to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee.

"(B) ACTION BY THE PEDIATRIC ADVISORY SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE.—Not later than 90 days after receiving a referral

under subparagraph (A), the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee shall—

"(i) review the available information on the safe and effective use of the drug in the pediatric population, including study reports submitted under this section; and

"(ii) make a recommendation to the Commissioner of Food and Drugs as to appropriate labeling changes, if any.

"(9) FDA DETERMINATION.—Not later than 30 days after receiving a recommendation from the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee under paragraph (8)(B)(ii) with respect to a drug, the Commissioner of Food and Drugs shall consider the recommendation and, if appropriate, make a request to the holders of approved applications for the drug to make any labeling change that the Commissioner of Food and Drugs determines to be appropriate.

"(10) FAILURE TO AGREE.—If a holder of an approved application for a drug, within 30 days after receiving a request to make a labeling change under paragraph (9), does not agree to make a requested labeling change, the Commissioner may deem the drug to be misbranded under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.).

"(11) NO EFFECT ON AUTHORITY.—Nothing in this subsection limits the authority of the United States to bring an enforcement action under the Federal Food, Drug, and Cosmetic Act when a drug lacks appropriate pediatric labeling. Neither course of action (the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee process or an enforcement action referred to in the preceding sentence) shall preclude, delay, or serve as the basis to stay the other course of action.

"(12) RECOMMENDATION FOR FORMULATION CHANGES.—If a pediatric study completed under public contract indicates that a formulation change is necessary and the Secretary agrees, the Secretary shall send a nonbinding letter of recommendation regarding that change to each holder of an approved application.

"(d) AUTHORIZATION OF APPROPRIATIONS.—

"(1) IN GENERAL.—There are authorized to be appropriated to carry out this section—

"(A) $200,000,000 for fiscal year 2002; and

"(B) such sums as are necessary for each of the five succeeding fiscal years.

"(2) AVAILABILITY.—Any amount appropriated under paragraph (1) shall remain available to carry out this section until expended.".

**SEC. 4. WRITTEN REQUEST TO HOLDERS OF APPROVED APPLICATIONS FOR DRUGS THAT HAVE MARKET EXCLUSIVITY.**

Section 505A(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(d)) is amended by adding at the end the following:

"(4) WRITTEN REQUEST TO HOLDERS OF APPROVED APPLICATIONS FOR DRUGS THAT HAVE MARKET EXCLUSIVITY.—

"(A) REQUEST AND RESPONSE.—If the Secretary makes a written request for pediatric studies (including neonates, as appropriate) under subsection (c) to the holder of an application approved under section 505(b)(1), the holder, not later than 180 days after receiving the written request, shall respond to the Secretary as to the intention of the holder to act on the request by—

"(i) indicating when the pediatric studies will be initiated, if the holder agrees to the request; or

"(ii) indicating that the holder does not agree to the request.

"(B) NO AGREEMENT TO REQUEST.—

"(i) REFERRAL.—If the holder does not agree to a written request within the time period specified in subparagraph (A), and if the Secretary determines that there is a continuing need for information relating to the use of the drug in the pediatric population (including neonates, as appropriate), the Secretary shall refer the drug to the Foundation for the National Institutes of Health established under section 499 of the Public Health Service Act (42 U.S.C. 290b) (referred to in this paragraph as the 'Foundation') for the conduct of the pediatric studies described in the written request.

"(ii) PUBLIC NOTICE.—The Secretary shall give public notice of the name of the drug, the name of the manufacturer, and the indications to be studied made in a referral under clause (i).

"(C) LACK OF FUNDS.—On referral of a drug under subparagraph (B)(i), the Foundation shall issue a proposal to award a grant to conduct the requested studies unless the Foundation certifies to the Secretary, within a timeframe that the Secretary determines is appropriate through guidance, that the Foundation does not have funds available under section 499(j)(9)(B)(i) to conduct the requested studies. If the Foundation so certifies, the Secretary shall refer the drug for inclusion on the list established under section 409I of the Public Health Service Act for the conduct of the studies.

"(D) EFFECT OF SUBSECTION.—Nothing in this subsection (including with respect to referrals from the Secretary to the Foundation) alters or amends section 301(j) of this Act or section 552 of title 5 or section 1905 of title 18, United States Code.

"(E) NO REQUIREMENT TO REFER.—Nothing in this subsection shall be construed to require that every declined written request shall be referred to the Foundation.

"(F) WRITTEN REQUESTS UNDER SUBSECTION (b).—For drugs under subsection (b) for which written requests have not been accepted, if the Secretary determines that there is a continuing need for information relating to the use of the drug in the pediatric population (including neonates, as appropriate), the Secretary shall issue a written request under subsection (c) after the date of approval of the drug.".

**SEC. 5. TIMELY LABELING CHANGES FOR DRUGS GRANTED EXCLUSIVITY; DRUG FEES.**

(a) ELIMINATION OF USER FEE WAIVER FOR PEDIATRIC SUPPLEMENTS.—Section 736(a)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379h(a)(1)) is amended—

(1) by striking subparagraph (F); and

(2) by redesignating subparagraph (G) as subparagraph (F).

(b) LABELING CHANGES.—

(1) DEFINITION OF PRIORITY SUPPLEMENT.—Section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321) is amended by adding at the end the following:

"(kk) PRIORITY SUPPLEMENT.—The term 'priority supplement' means a drug application referred to in section 101(4) of the Food and Drug Administration Modernization Act of 1997 (111 Stat. 2298).".

(2) TREATMENT AS PRIORITY SUPPLEMENTS.—Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) is amended by adding at the end the following:

"(l) LABELING SUPPLEMENTS.—

"(1) PRIORITY STATUS FOR PEDIATRIC SUPPLEMENTS.—Any supplement to an application under section 505 proposing a labeling change pursuant to a report on a pediatric study under this section—

"(A) shall be considered to be a priority supplement; and

"(B) shall be subject to the performance goals established by the Commissioner for priority drugs.

"(2) DISPUTE RESOLUTION.—

"(A) REQUEST FOR LABELING CHANGE AND FAILURE TO AGREE.—If the Commissioner determines that an application with respect to which a pediatric study is conducted under this section is approvable and that the only open issue for final action on the application is the reaching of an agreement between the sponsor of the application and the Commissioner on appropriate changes to the labeling for the drug that is the subject of the application, not later than 180 days after the date of submission of the application—

"(i) the Commissioner shall request that the sponsor of the application make any labeling change that the Commissioner determines to be appropriate; and

"(ii) if the sponsor of the application does not agree to make a labeling change requested by the Commissioner, the Commissioner shall refer the matter to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee.

"(B) ACTION BY THE PEDIATRIC ADVISORY SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE.—Not later than 90 days after receiving a referral under subparagraph (A)(ii), the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee shall—

"(i) review the pediatric study reports; and

"(ii) make a recommendation to the Commissioner concerning appropriate labeling changes, if any.

"(C) CONSIDERATION OF RECOMMENDATIONS.—The Commissioner shall consider the recommendations of the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee and, if appropriate, not later than 30 days after receiving the recommendation, make a request to the sponsor of the application to make any labeling change that the Commissioner determines to be appropriate.

"(D) MISBRANDING.—If the sponsor of the application, within 30 days after receiving a request under subparagraph (C), does not agree to make a labeling change requested by the Commissioner, the Commissioner may deem the drug that is the subject of the application to be misbranded.

"(E) NO EFFECT ON AUTHORITY.—Nothing in this subsection limits the authority of the United States to bring an enforcement action under this Act when a drug lacks appropriate pediatric labeling. Neither course of action (the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee process or an enforcement action referred to in the preceding sentence) shall preclude, delay, or serve as the basis to stay the other course of action.".

**SEC. 6. OFFICE OF PEDIATRIC THERAPEUTICS.**

(a) ESTABLISHMENT.—The Secretary of Health and Human Services shall establish an Office of Pediatric Therapeutics within the Food and Drug Administration.

(b) DUTIES.—The Office of Pediatric Therapeutics shall be responsible for coordination and facilitation of all activities of the Food and Drug Administration that may have any effect on a pediatric population or the practice of pediatrics or may in any other way involve pediatric issues.

(c) STAFF.—The staff of the Office of Pediatric Therapeutics shall coordinate with employees of the Department of Health and Human Services who exercise responsibilities relating to pediatric therapeutics and shall include—

(1) one or more additional individuals with expertise concerning ethical issues presented by the conduct of clinical research in the pediatric population; and

(2) one or more additional individuals with expertise in pediatrics as may be necessary to perform the activities described in subsection (b).

**SEC. 7. NEONATES.**

Section 505A(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(g)) is amended by inserting "(including neonates in appropriate cases)" after "pediatric age groups".

**SEC. 8. SUNSET.**

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) is amended by striking subsection (j) and inserting the following:

"(j) SUNSET.—A drug may not receive any 6-month period under subsection (a) or (c) unless—

"(1) on or before October 1, 2007, the Secretary makes a written request for pediatric studies of the drug;

"(2) on or before October 1, 2007, an application for the drug is accepted for filing under section 505(b); and

"(3) all requirements of this section are met.".

**SEC. 9. DISSEMINATION OF PEDIATRIC INFORMATION.**

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) (as amended by section 5(b)(2)) is amended by adding at the end the following:

"(m) DISSEMINATION OF PEDIATRIC INFORMATION.—

"(1) IN GENERAL.—Not later than 180 days after the date of submission of a report on a pediatric study under this section, the Commissioner shall make available to the public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted for the supplement, including by publication in the Federal Register.

"(2) EFFECT OF SUBSECTION.—Nothing in this subsection alters or amends section 301(j) of this Act or section 552 of title 5 or section 1905 of title 18, United States Code.".

**SEC. 10. CLARIFICATION OF INTERACTION OF PEDIATRIC EXCLUSIVITY UNDER SECTION 505A OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT AND 180-DAY EXCLUSIVITY AWARDED TO AN APPLICANT FOR APPROVAL OF A DRUG UNDER SECTION 505(j) OF THAT ACT.**

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) (as amended by section 9) is amended by adding at the end the following:

"(n) CLARIFICATION OF INTERACTION OF MARKET EXCLUSIVITY UNDER THIS SECTION AND MARKET EXCLUSIVITY AWARDED TO AN APPLICANT FOR APPROVAL OF A DRUG UNDER SECTION 505(j).—If a 180-day period under section 505(j)(5)(B)(iv) overlaps with a 6-month exclusivity period under this section, so that the applicant for approval of a drug under section 505(j) entitled to the 180-day period under that section loses a portion of the 180-day period to which the applicant is entitled for the drug, the 180-day period shall be extended from—

"(1) the date on which the 180-day period would have expired by the number of days of the overlap, if the 180-day period would, but for the application of this subsection, expire after the 6-month exclusivity period; or

"(2) the date on which the 6-month exclusivity period expires, by the number of days of the overlap if the 180-day period would, but for the application of this subsection, expire during the six-month exclusivity period.".

**SEC. 11. PROMPT APPROVAL OF DRUGS UNDER SECTION 505(j) WHEN PEDIATRIC INFORMATION IS ADDED TO LABELING.**

(a) IN GENERAL.—Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) (as amended by section 10) is amended by adding at the end the following:

"(o) PROMPT APPROVAL OF DRUGS UNDER SECTION 505(j) WHEN PEDIATRIC INFORMATION IS ADDED TO LABELING.—

"(1) GENERAL RULE.—A drug for which an application has been submitted or approved under section 505(j) shall not be considered ineligible for approval under that section or misbranded under section 502 on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling pertaining to pediatric use when the omitted indication

or other aspect is protected by patent or by exclusivity under clause (iii) or (iv) of section 505(j)(5)(D).

"(2) LABELING.—Notwithstanding clauses (iii) and (iv) of section 505(j)(5)(D), the Secretary may require that the labeling of a drug approved under section 505(j) that omits a pediatric indication or other aspect of labeling as described in paragraph (1) include—

"(A) a statement that, because of marketing exclusivity for a manufacturer—

"(i) the drug is not labeled for pediatric use; or

"(ii) in the case of a drug for which there is an additional pediatric use not referred to in paragraph (1), the drug is not labeled for the pediatric use under paragraph (1); and

"(B) a statement of any appropriate pediatric contraindications, warnings, or precautions that the Secretary considers necessary.

"(3) PRESERVATION OF PEDIATRIC EXCLUSIVITY AND OTHER PROVISIONS.—This subsection does not affect—

"(A) the availability or scope of exclusivity under this section;

"(B) the availability or scope of exclusivity under section 505 for pediatric formulations;

"(C) the question of the eligibility for approval of any application under section 505(j) that omits any other conditions of approval entitled to exclusivity under clause (iii) or (iv) of section 505(j)(5)(D); or

"(D) except as expressly provided in paragraphs (1) and (2), the operation of section 505.".

(b) EFFECTIVE DATE.—The amendment made by subsection (a) takes effect on the date of enactment of this Act, including with respect to applications under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)) that are approved or pending on that date.

**SEC. 12. STUDY CONCERNING RESEARCH INVOLVING CHILDREN.**

(a) CONTRACT WITH INSTITUTE OF MEDICINE.—The Secretary of Health and Human Services shall enter into a contract with the Institute of Medicine for—

(1) the conduct, in accordance with subsection (b), of a review of—

(A) Federal regulations in effect on the date of the enactment of this Act relating to research involving children;

(B) federally prepared or supported reports relating to research involving children; and

(C) federally supported evidence-based research involving children; and

(2) the submission to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives, not later than two years after the date of enactment of this Act, of a report concerning the review conducted under paragraph (1) that includes recommendations on best practices relating to research involving children.

(b) AREAS OF REVIEW.—In conducting the review under subsection (a)(1), the Institute of Medicine shall consider the following:

(1) The written and oral process of obtaining and defining "assent", "permission" and "informed consent" with respect to child clinical research participants and the parents, guardians, and the individuals who may serve as the legally authorized representatives of such children (as defined in subpart A of part 46 of title 45, Code of Federal Regulations).

(2) The expectations and comprehension of child research participants and the parents, guardians, or legally authorized representatives of such children, for the direct benefits and risks of the child's research involvement, particularly in terms of research versus therapeutic treatment.

(3) The definition of "minimal risk" with respect to a healthy child or a child with an illness.

(4) The appropriateness of the regulations applicable to children of differing ages and maturity levels, including regulations relating to legal status.

(5) Whether payment (financial or otherwise) may be provided to a child or his or her parent, guardian, or legally authorized representative for the participation of the child in research, and if so, the amount and type of payment that may be made.

(6) Compliance with the regulations referred to in subsection (a)(1)(A), the monitoring of such compliance (including the role of institutional review boards), and the enforcement actions taken for violations of such regulations.

(7) The unique roles and responsibilities of institutional review boards in reviewing research involving children, including composition of membership on institutional review boards.

(c) REQUIREMENTS OF EXPERTISE.—The Institute of Medicine shall conduct the review under subsection (a)(1) and make recommendations under subsection (a)(2) in conjunction with experts in pediatric medicine, pediatric research, and the ethical conduct of research involving children.

**SEC. 13. FOUNDATION FOR THE NATIONAL INSTITUTES OF HEALTH.**

Section 499 of the Public Health Service Act (42 U.S.C. 290b) is amended—

(1) in subsection (b), by inserting "(including collection of funds for pediatric pharmacologic research)" after "mission";

(2) in subsection (c)(1)—

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

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

"(C) A program to collect funds for pediatric pharmacologic research and studies listed by the Secretary pursuant to section 409I(a)(1)(A) of this Act and referred under section 505A(d)(4)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(d)(4)(C)).";

(3) in subsection (d)—

(A) in paragraph (1)—

(i) in subparagraph (B)—

(I) in clause (ii), by striking "and" at the end;

(II) in clause (iii), by striking the period and inserting "; and"; and

(III) by adding at the end the following:

"(iv) the Commissioner of Food and Drugs."; and

(ii) by striking subparagraph (C) and inserting the following:

"(C) The ex officio members of the Board under subparagraph (B) shall appoint to the Board individuals from among a list of candidates to be provided by the National Academy of Science. Such appointed members shall include—

"(i) representatives of the general biomedical field;

"(ii) representatives of experts in pediatric medicine and research;

"(iii) representatives of the general biobehavioral field, which may include experts in biomedical ethics; and

"(iv) representatives of the general public, which may include representatives of affected industries."; and

(B) in paragraph (2), by realigning the margin of subparagraph (B) to align with subparagraph (A);

(4) in subsection (k)(9)—

(A) by striking "The Foundation" and inserting the following:

"(A) IN GENERAL.—The Foundation"; and

(B) by adding at the end the following:

"(B) GIFTS, GRANTS, AND OTHER DONATIONS.—

"(i) IN GENERAL.—Gifts, grants, and other donations to the Foundation may be designated for pediatric research and studies on drugs, and funds so designated shall be used solely for grants for research and studies under subsection (c)(1)(C).

"(ii) OTHER GIFTS.—Other gifts, grants, or donations received by the Foundation and not described in clause (i) may also be used to support such pediatric research and studies.

"(iii) REPORT.—The recipient of a grant for research and studies shall agree to provide the Director of the National Institutes of Health and the Commissioner of Food and Drugs, at the conclusion of the research and studies—

"(I) a report describing the results of the research and studies; and

"(II) all data generated in connection with the research and studies.

"(iv) ACTION BY THE COMMISSIONER OF FOOD AND DRUGS.—The Commissioner of Food and Drugs shall take appropriate action in response to a report received under clause (iii) in accordance with paragraphs (7) through (12) of section 409I(c), including negotiating with the holders of approved applications for the drugs studied for any labeling changes that the Commissioner determines to be appropriate and requests the holders to make.

"(C) APPLICABILITY.—Subparagraph (A) does not apply to the program described in subsection (c)(1)(C).";

(5) by redesignating subsections (f) through (m) as subsections (e) through (l), respectively;

(6) in subsection (h)(11) (as so redesignated), by striking "solicit" and inserting "solicit,"; and

(7) in paragraphs (1) and (2) of subsection (j) (as so redesignated), by striking "(including those developed under subsection (d)(2)(B)(i)(II))" each place it appears.

**SEC. 14. PEDIATRIC PHARMACOLOGY ADVISORY COMMITTEE.**

(a) IN GENERAL.—The Secretary of Health and Human Services shall, under section 222 of the Public Health Service Act (42 U.S.C. 217a), convene and consult an advisory committee on pediatric pharmacology (referred to in this section as the "advisory committee").

(b) PURPOSE.—

(1) IN GENERAL.—The advisory committee shall advise and make recommendations to the Secretary, through the Commissioner of Food and Drugs and in consultation with the Director of the National Institutes of Health, on matters relating to pediatric pharmacology.

(2) MATTERS INCLUDED.—The matters referred to in paragraph (1) include—

(A) pediatric research conducted under sections 351, 409I, and 499 of the Public Health Service Act and sections 501, 502, 505, and 505A of the Federal Food, Drug, and Cosmetic Act;

(B) identification of research priorities related to pediatric pharmacology and the need for additional treatments of specific pediatric diseases or conditions; and

(C) the ethics, design, and analysis of clinical trials related to pediatric pharmacology.

(c) COMPOSITION.—The advisory committee shall include representatives of pediatric health organizations, pediatric researchers, relevant patient and patient-family organizations, and other experts selected by the Secretary.

**SEC. 15. PEDIATRIC SUBCOMMITTEE OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE.**

(a) CLARIFICATION OF AUTHORITIES.—

(1) IN GENERAL.—The Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (referred to in this section as the "Subcommittee"), in carrying out the mission of reviewing and evaluating the data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of pediatric cancers, shall—

(A) evaluate and, to the extent practicable, prioritize new and emerging therapeutic alternatives available to treat pediatric cancer;

(B) provide recommendations and guidance to help ensure that children with cancer have timely access to the most promising new cancer therapies; and

(C) advise on ways to improve consistency in the availability of new therapeutic agents.

(2) MEMBERSHIP.—

(A) IN GENERAL.—The Secretary shall appoint not more than 11 voting members to the Pediatric Subcommittee from the membership of the Pediatric Pharmacology Advisory Committee and the Oncologic Drugs Advisory Committee.

(B) REQUEST FOR PARTICIPATION.—The Subcommittee shall request participation of the following members in

the scientific and ethical consideration of topics of pediatric cancer, as necessary:

(i) At least two pediatric oncology specialists from the National Cancer Institute.

(ii) At least four pediatric oncology specialists from—

(I) the Children's Oncology Group;

(II) other pediatric experts with an established history of conducting clinical trials in children; or

(III) consortia sponsored by the National Cancer Institute, such as the Pediatric Brain Tumor Consortium, the New Approaches to Neuroblastoma Therapy or other pediatric oncology consortia.

(iii) At least two representatives of the pediatric cancer patient and patient-family community.

(iv) One representative of the nursing community.

(v) At least one statistician.

(vi) At least one representative of the pharmaceutical industry.

(b) PRE-CLINICAL MODELS TO EVALUATE PROMISING PEDIATRIC CANCER THERAPIES.—Section 413 of the Public Health Service Act (42 U.S.C. 285a–2) is amended by adding at the end the following:

"(c) PRE-CLINICAL MODELS TO EVALUATE PROMISING PEDIATRIC CANCER THERAPIES.—

"(1) EXPANSION AND COORDINATION OF ACTIVITIES.—The Director of the National Cancer Institute shall expand, intensify, and coordinate the activities of the Institute with respect to research on the development of preclinical models to evaluate which therapies are likely to be effective for treating pediatric cancer.

"(2) COORDINATION WITH OTHER INSTITUTES.—The Director of the Institute shall coordinate the activities under paragraph (1) with similar activities conducted by other national research institutes and agencies of the National Institutes of Health to the extent that those Institutes and agencies have responsibilities that are related to pediatric cancer.".

(c) CLARIFICATION OF AVAILABILITY OF INVESTIGATIONAL NEW DRUGS FOR PEDIATRIC STUDY AND USE.—

(1) AMENDMENT OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.—Section 505(i)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(1)) is amended—

(A) in subparagraph (B), by striking "and" at the end;

(B) in subparagraph (C), by striking the period at the end and inserting "; and"; and

(C) by adding at the end the following:

"(D) the submission to the Secretary by the manufacturer or the sponsor of the investigation of a new drug of a statement of intent regarding whether the manufacturer or sponsor has plans for assessing pediatric safety and efficacy.".

(2) AMENDMENT OF THE PUBLIC HEALTH SERVICE ACT.—Section 402(j)(3)(A) of the Public Health Service Act (42 U.S.C. 282(j)(3)(A)) is amended in the first sentence—

(A) by striking "trial sites, and" and inserting "trial sites,"; and

(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;