

THE FOOD AND DRUG ADMINISTRATION AMENDMENTS ACT OF 2007

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On 27 September 2007, the President signed into law the Food and Drug Administration Amendments Act of 2007 ('FDAAA'). This law, containing 11 titles, reauthorises and amends both the prescription drug user fee programme and the medical device user fee programme. It also reauthorises and amends the pediatric exclusivity and pediatric assessment programmes applicable to new drugs. It contains new provisions intended to provide incentives to device manufacturers to create medical devices specifically designed to meet the needs of pediatric patients. It provides the Food and Drug Administration ('FDA') with enhanced authority regarding the safety of approved drugs, expands the National Institutes of Health ('NIH') registry of clinical trials, requires the creation of a database for results of those trials, and addresses conflicts of interest on FDA advisory committees. Another title addresses the safety of human and pet food. The law contains a variety of additional amendments to the Federal Food, Drug, and Cosmetic Act ('FDCA').

This article summarises the most significant provisions of the FDAAA applicable to drugs and medical devices.

Title I: Prescription Drug User Fee Amendments of 2007

Title I of the FDAAA reauthorises and amends FDA's prescription drug user fee programme through fiscal year 2012.¹ Among the changes to the programme are a general increase in the fees to be paid and revised workload and inflation adjusters, which are expected to increase fees

further in future years, subject to certain caps. The new law allows user fees to be used for postmarket drug safety activities for all products without time limitation, extends user fees to all 505(b)(2) applications, and exempts qualifying orphan drugs from annual establishment and product fees.

A new section 736A of the FDCA authorises FDA to assess user fees for the review of direct-to-consumer ('DTC') television advertising voluntarily submitted to the Agency for advisory review prior to broadcast. This programme is authorised through fiscal year 2012.

The FDA performance goals that will apply to the reauthorised user fee programme and advisory review of DTC television advertisements are set out in a 'goals letter'.² The basic performance goals for review of standard and priority new drug applications ('NDAs') and biologics licence applications ('BLAs') are unchanged. New goals have been established for review of proposed proprietary drug names and actions to enhance and modernise the drug safety system. In addition, FDA commits to making a decision within a certain number of days on a certain percentage of DTC television advertisements submitted to the Agency.

Title II: Medical Device User Fee Amendments of 2007

Subtitle A: Fees Related to Medical Devices

This subtitle reauthorises and amends FDA's medical device user fee programme through fiscal year 2012.³ Among the most significant changes to the programme are a reduction in most existing user fees for medical device submissions, an expansion of the programme to provide fees for additional submissions, and authorisation of an annual establishment fee for manufacturers, single-use device reproducers, and specification developers. The new law also reduces user fees paid by small businesses and authorises additional appropriations for postmarket safety information on medical devices.

The performance goals that apply to the reauthorised medical device user fee programme are described in a 'goals letter'.⁴ FDA is eliminating all cycle goals (for example, actions prior to final decisions on submissions such as deficiency letters) included as part of the previous performance goal structure and is implementing two-tiered decision goals (for example, decisions to approve or not to approve an application). FDA is also committing to a number of qualitative goals aimed at enhancing the premarket review process such as facilitating the timely scheduling of meetings.

1) FDCA section 736.

2) 153 Cong. Rec. S12421-428 (Oct. 2, 2007).

3) FDCA section 738.

4) 153 Cong. Rec. S12420-421 (Oct. 2, 2007).

Subtitle B: Amendments Regarding Regulation of Medical Devices

This subtitle includes a number of changes to programmes affecting the regulation of medical devices and requires the establishment of a unique device identification system for medical devices.

Registration of Device Establishments and Device Listing

Section 222 of the FDAAA amends section 510 of the FDCA to require any establishment engaged in manufacturing devices to register annually between 1 October and 31 December.⁵ Previously, device establishments were required to register on or before 31 December each year. In addition, each registered device establishment must file its device list (of devices being manufactured for commercial distribution) once a year between 1 October and 31 December, rather than twice a year as required previously.⁶ Registration and listing must be done electronically unless FDA grants a waiver.

Unique Device Identification System

Section 226 of the FDAAA amends section 519 of the FDCA to require FDA to publish regulations establishing a unique device identification system for medical devices.⁷ Under any system proposed by FDA, device labels must bear a unique device identifier ('UDI'), unless the Agency permits an alternate placement of the UDI or provides for an exception for a particular device or type of devices. No timeline for implementation accompanies this provision.

Inspections by Accredited Persons

Section 228 of the FDAAA modifies the accredited person ('AP') inspection programme established under section 704(g) of the FDCA. Under the new law, a device establishment is eligible for inspection by an AP if the results of its most recent inspections were classified as 'no action indicated' or 'voluntary action indicated' and the establishment notifies FDA of its intent to use an AP within 30 days of the inspection.⁸ FDA may request from the owner or operator of the establishment submitting a notice or the AP identified in the notice data concerning compliance with FDA's current good manufacturing practices or information concerning the relationship between the owner or operator of the establishment and the AP identified in the notice.⁹ If FDA does not respond to the submitted information within 60 days, the establishment is deemed to have clearance to participate in the programme.¹⁰

Under the new law, manufacturers may also voluntarily submit audit reports by third parties assessing conformity with appropriate quality system standards such as the International Organization for Standardization ('ISO').¹¹ FDA will consider this information when setting its risk-based inspectional priorities.

Title III: Pediatric Medical Device Safety and Improvement Act of 2007

This title contains provisions designed to provide incentives to device manufacturers to create medical devices specifically designed to meet the needs of pediatric patients.

Tracking Pediatric Device Approvals

Section 302 of the FDAAA adds FDCA section 515A, which is aimed at improving the way FDA tracks the number and types of devices approved for use in children or for conditions that occur in children. In particular, applications for humanitarian device exemptions ('HDEs'), premarket applications ('PMAs'), supplements to PMAs, and product development protocols must now include, if the information is 'readily available', a description of any pediatric subpopulations (for example, neonates, infants, children, and adolescents) that suffer from the disease or condition that the device is intended to treat, diagnose or cure and the number of pediatric patients affected by the disease or condition. Section 515A also requires FDA to track data regarding the use, review, and approval of pediatric devices and submit this information in an annual report to Congress.¹²

Modification to Humanitarian Device Exemption

Section 303 of the FDAAA modifies the existing HDE for medical devices under section 520(m) of the FDCA to allow manufacturers of HDE-approved devices labelled for use in pediatric patients to make a profit from the sales of those devices.¹³ To qualify for this exception, the device must not have been previously approved under section 520(m) for pediatric use prior to enactment of the FDAAA, and the number of devices distributed during any calendar year must not exceed the annual distribution number set by FDA when the HDE is granted unless a waiver is provided.

5) FDCA section 510(b)(2). Section 222 of the FDAAA also requires a foreign manufacturer of a device imported or offered for import into the United States to register immediately with the Secretary 'upon first engaging in any such activity' and annually thereafter between 1 October and 31 December. *Ibid.*, section 510(i)(1).

6) *Ibid.*, section 510(j)(2).

7) *Ibid.*, section 519(f).

8) *Ibid.*, section 704(g)(6)(A).

9) *Ibid.*, section 704(g)(6)(B)(ii).

10) *Ibid.*, section 704(g)(6)(B)(iv).

11) *Ibid.*, section 704(g)(7)(F).

12) *Ibid.*, section 515A(a).

13) *Ibid.*, section 520(m)(6)(A).

The Secretary of Health and Human Services ('HHS') must refer any report of an adverse event for a pediatric HDE device to the Office of Pediatric Therapeutics.¹⁴ The Pediatric Advisory Committee must review a report periodically and make recommendations as to whether the Secretary should take action in response to a report. The Pediatric Advisory Committee must also conduct an annual review of all pediatric HDE devices to determine whether the exemption is still appropriate.¹⁵

Encouraging Pediatric Medical Device Research

Section 304 of the FDAAA amends section 402(b) of the Public Health Service Act ('PHSA') to require NIH to designate a 'contact point or office' to help innovators and physicians identify sources of funding for pediatric medical device development.¹⁶ NIH, FDA, and the Agency for Health Research and Quality ('AHRQ') must also work together to create a plan for expanding pediatric medical device research and development.

Demonstration Grants for Improving Pediatric Device Availability

Section 305 of the FDAAA authorises HHS to award \$6 million in demonstration grants annually from fiscal years 2008 to 2012 to nonprofit consortia, to facilitate the development, production, and distribution of pediatric devices.

Amendments to Office of Pediatric Therapeutics and Pediatric Advisory Committee

Section 306 of the FDAAA amends section 6(b) of the Best Pharmaceuticals for Children Act ('BPCA') to expand the responsibilities of the Office of Pediatric Therapeutics to include the co-ordination and facilitation of all activities of FDA involving increasing pediatric access to medical devices. Section 306 also amends section 14 of the BPCA to require the Pediatric Advisory Committee to advise and make recommendations to FDA on matters relating to medical devices for pediatric use.

Postmarket Surveillance

Section 307 of the FDAAA amends section 522 of the FDCA to permit FDA to order a manufacturer to conduct postmarket

surveillance for any class II or class III device that is expected to have 'significant use' in pediatric populations.¹⁷ In addition, in order to assess the impact of the device on a child's growth and development, FDA may now require surveillance for longer than three years.¹⁸ Previously, FDA could not order a manufacturer to conduct surveillance for more than three years. Manufacturers may request review of any order or condition requiring postmarket surveillance through FDA's dispute resolution process.¹⁹

Title IV: Pediatric Research Equity Act of 2007

Section 402 of the FDAAA reauthorises and modifies the mandatory pediatric study provisions of the Pediatric Research Equity Act ('PREA').²⁰ The provisions of the amended PREA generally apply to any pediatric assessment pending at the time of enactment (including deferred assessments).

Assessment Requirements

New Drug and Biologics Licence Applications

Under the amended PREA, just as before, any person that submits a new drug or biologics licence application to market a new active ingredient, a new indication, a new dosage form, a new dosing regimen, or a new route of administration must include a pediatric assessment. A pediatric assessment must contain data adequate to assess the safety and effectiveness of the product for its claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. If FDA determines that studies are not needed in each pediatric subpopulation because the data from one subpopulation can be extrapolated to other subpopulations, the statute now requires documentation of the scientific data supporting the Agency's decision.²¹

The revised PREA also requires FDA to make the medical, statistical, and clinical pharmacology reviews of a pediatric assessment available to the public in an easily accessible manner, including through the FDA website, within 210 days after the date of submission of the assessment.²² This requirement does not 'alter or amend' section 301(j) of the FDCA (which protects trade secrets), the Freedom of Information Act ('FOIA'), or the Federal Trade Secrets Act.²³

14) *Ibid.*, section 520(m)(7).

15) *Ibid.*, section 520(m)(8).

16) PHSA section 402(b)(23).

17) FDCA section 522(a).

18) *Ibid.*, section 522(b)(2).

19) *Ibid.*, section 522(c).

20) *Ibid.*, section 505B.

21) *Ibid.*, section 505B(a)(2)(B)(iii).

22) *Ibid.*, section 505B(h)(1).

23) *Ibid.*, section 505B(h)(3).

Already Marketed Drugs

Under the amended PREA, as before, FDA may require the holder of an already approved NDA or BLA to submit pediatric assessments under certain circumstances. The revised PREA, however, lowers somewhat and streamlines the standards to invoke this authority. In particular, in order for FDA to mandate pediatric assessments for already marketed products, the Agency must now find that: (1) the absence of adequate pediatric labelling could pose a risk to pediatric patients; (2) there is reason to believe the product would represent a meaningful therapeutic benefit over existing therapies for pediatric patients for one or more of the claimed indications; or (3) the product is used for a substantial number of pediatric patients for the labelled indications, and adequate pediatric labelling could confer a benefit on pediatric patients.²⁴

Deferrals

The amended PREA also retains FDA's authority to defer the requirement for pediatric information in a new application or supplement on the Agency's own initiative or at the request of the applicant. The applicant must now submit a timeline for completion of the studies as part of any request for deferral.²⁵ The amended PREA also requires annual submission of information detailing progress made in conducting the pediatric studies and, if no progress has been made, evidence and documentation that the studies 'will be conducted with due diligence and at the earliest possible time'.²⁶ The annual progress submission must be made publicly accessible, including through the FDA website.

Waivers

Under the amended PREA, as before, FDA may grant a full or partial waiver of a pediatric assessment for a new drug or biological product or an already marketed drug. An applicant seeking a full or partial waiver on the ground that a pediatric formulation is not possible, however, must now submit information detailing why the formulation cannot be developed.²⁷ If the waiver is granted, this information must be made available to the public promptly, including through the FDA website. If either a full or partial waiver is granted because of evidence that the product would be ineffective or unsafe in pediatric patients or in a pediatric subpopulation, that information must be included in the product's labelling.²⁸

Internal Review Committee

Section 403 of the FDATA creates a new section 505(C), establishing an internal FDA committee to review pediatric plans, assessments, deferrals, and waivers. FDA must use the internal committee to provide consultation to reviewing divisions on all pediatric plans and assessments prior to approval of an application or supplement for which a pediatric assessment is required and all deferral and waiver requests granted under the PREA.²⁹ Within one year of the date of enactment, the committee must conduct a retrospective review and analysis of a representative sample of assessments submitted and deferrals and waivers approved since enactment of the original Pediatric Research Equity Act in 2003. FDA, in consultation with the committee, must track and make available to the public, through its website, information pertaining to pediatric assessments and labelling changes.

Labelling Changes

If the sponsor of an application or supplement and the FDA are unable to agree on labelling changes, the amended PREA provides a dispute resolution process similar to that mandated under the BPCA.³⁰

In addition, if FDA determines that a pediatric assessment does or does not demonstrate that the drug is safe and effective in pediatric populations or subpopulations, including whether the assessment results are inconclusive, the Agency must order that the drug's 'label' include information about the results of an assessment and a statement of the Agency's determination.³¹

Adverse Event Reporting

During the one-year period beginning on the date a labelling change is made related to a pediatric assessment, FDA must ensure that all adverse event reports that have been received for the drug are referred to the Office of Pediatric Therapeutics.³² The Pediatric Advisory Committee must review the reports and make recommendations to the Director of the Office. Following the one-year period, FDA must, as appropriate, refer to the Office of Pediatric Therapeutics all pediatric adverse event reports for the drug.³³

24) *Ibid.*, section 505B(b)(1).

25) *Ibid.*, section 505B(a)(3)(A)(i)(IV).

26) *Ibid.*, section 505B(a)(3)(B).

27) *Ibid.*, section 505B(a)(4)(C), (b)(2)(C).

28) *Ibid.*, section 505B(a)(4)(D), (b)(2)(D).

29) *Ibid.*, section 505B(f).

30) *Ibid.*, section 505B(g)(1).

31) *Ibid.*, section 505B(g)(2).

32) *Ibid.*, section 505B(i)(1).

33) *Ibid.*, section 505B(i)(2).

Title V: Best Pharmaceuticals for Children Act of 2007

Section 502 of the FDAAA reauthorises the pediatric exclusivity and NIH pediatric study provisions of the BPCA with modifications. In general, the amendments to the new BPCA apply to written requests issued by FDA on or after 27 September 2007.

Marketing Exclusivity

The amended BPCA retains the six-month pediatric exclusivity provision as an incentive for sponsors and holders of applications for new drugs to conduct studies regarding the use of drugs in children. Now, however, pediatric exclusivity will be applied to an existing patent or exclusivity period only where FDA accepts the pediatric studies and awards pediatric exclusivity at least nine months prior to the expiry of the patent or exclusivity period in question.³⁴

Written Requests

As before, in order to earn exclusivity, the applicant or application holder must conduct its study or studies in response to a written request from FDA. As amended, the law states explicitly that FDA's request may relate to more than one use of a drug, may include preclinical studies, and may relate to unapproved uses.³⁵

As before, an applicant or application holder must accept or decline FDA's written request within 180 days of receiving the request. If the applicant or holder declines the request, the revised BPCA requires the response to include the reason for declining the request.³⁶ Further, if the applicant or holder declines the request on the grounds that it is not possible to develop an appropriate pediatric formulation, it must provide the reasons the pediatric formulation cannot be developed.³⁷

FDA now has 180 days, rather than 90 days, to accept or reject pediatric submissions.³⁸ Also, within 210 days after submission of the report, FDA must make available to the public the medical, statistical and clinical pharmacology reviews of the pediatric study. This requirement does not alter or amend FOIA, section 301(j) of the FDCA, or the Federal Trade Secrets Act.³⁹

Notice of Determination

The amended BPCA requires that within 30 days of accepting a pediatric report, FDA must publish a notice that the Agency has accepted a pediatric report under the BPCA and that the applicant will receive pediatric exclusivity.⁴⁰ Previously, no time period for publication was specified. Under the new law, the notice must include a copy of FDA's written request for the studies. Also, FDA must publish a notice identifying any drug for which, on or after 27 September 2007, a pediatric formulation was developed, studied, and found to be safe and effective in the pediatric population (or subpopulation), if the pediatric formulation for the drug is not introduced onto the market within one year after the date that FDA publishes notice that the report was accepted.⁴¹

Internal Review of Written Requests and Pediatric Studies

FDA must use the new pediatric internal committee established under FDCA section 505C to review all written requests issued under the BPCA on or after 27 September 2007, prior to issuance of those requests.⁴² The committee may also review studies conducted under the BPCA to make a recommendation to the Secretary whether to accept or reject the reports. FDA, in consultation with the committee, must track and make publicly available, including through its website, information regarding pediatric studies and labelling changes.

Labelling Changes

The amended BPCA retains the dispute resolution process, with minor changes, for sponsors and FDA to follow when they are unable to agree on labelling changes.⁴³ The amended law permits FDA to order a label change in certain. Specifically, if, on or after 27 September 2007, FDA determines that a pediatric study conducted under section 505A does or does not demonstrate that the drug is safe and effective in pediatric populations or subpopulations, including whether the study results are inconclusive, the Agency must order that the drug's 'label' include information about the results of the study and a statement of the Agency's determination.⁴⁴

34) *Ibid.*, section 505A(b)(2), (c)(2).

35) *Ibid.*, section 505A(d)(1)(B).

36) *Ibid.*, section 505A(d)(2)(A)(i)(II).

37) *Ibid.*, section 505A(d)(2)(A)(ii).

38) *Ibid.*, section 505A(d)(3).

39) *Ibid.*, section 505A(k).

40) *Ibid.*, section 505A(e)(1).

41) *Ibid.*, section 505A(e)(2).

42) *Ibid.*, section 505A(f).

43) *Ibid.*, section 505A(i)(2).

44) *Ibid.*, section 505A(j).

Adverse Event Reporting

The amended BPCA includes a process for reporting adverse events similar to the process described under the amended PREA.⁴⁵

Referral if Pediatric Studies Not Completed

The new BPCA includes a streamlined process for the FDA to refer to drugs to the NIH for study or to invoke its mandatory study authority where a sponsor does not conduct studies under the pediatric exclusivity provisions.⁴⁶

NIH Programme for Pediatric Studies of Drugs

Within one year of enactment, NIH must develop and publish a priority list of needs in pediatric therapeutics, including drugs or indications that require study.⁴⁷ The list must be revised every three years. NIH must award available funds to entities to conduct the studies in question or other research on these issues.⁴⁸

NIH must submit proposed pediatric study requests to the FDA for pediatric studies of a specific pediatric indication identified on the priority list.⁴⁹ Based on the proposed request, FDA may issue a written request to every holder of an approved application for the drug under section 505 of the FDCA. The request must include a timeframe for negotiations for an agreement and must be made in a manner equivalent to the manner in which a written request is made under the BPCA.

If FDA does not receive a response to the written request within 30 days, NIH must publish a request for proposals to conduct the pediatric studies described in the written request. NIH may award a contract, grant, or other funding to conduct the studies only if a proposal is submitted in such form and manner, and containing such agreements, assurances, and information as NIH determines is necessary to carry out the study. On completion of a pediatric study in accordance with an award under this section of the PHSA, a report containing all data generated in connection with the study must be submitted to NIH and FDA. The report will be considered to be in the public domain and must be assigned a docket number by FDA.

Within 180 days of receiving the report, FDA must review the report and any other data available concerning the safe and effective use of the drug in the pediatric population studied;

negotiate with the application holders regarding any labelling changes that the Agency determines to be appropriate and requests the holders to make; place in the public docket file a copy of the report and any requested labelling changes; and publish in the Federal Register and post on the FDA website a summary of the report and a copy of any requested labelling changes.

The new law also mandates a dispute resolution process similar to the dispute resolution process included under the PREA or BPCA if an application holder does not agree to the labeling changes requested by FDA.

Title VI: Reagan-Udall Foundation

Reagan-Udall Foundation

Section 601 of the FDAAA adds sections 770 to 772 to the FDCA, establishing a nonprofit corporation, the Reagan-Udall Foundation for the Food and Drug Administration. The Foundation will serve to modernise medical, veterinary, food, food ingredient, and cosmetic product development; accelerate innovation; and enhance product safety.

Office of the Chief Scientist

Section 602 adds section 910 to the FDCA, creating an Office of the Chief Scientist within the Office of the Commissioner to oversee and ensure the quality and regulatory focus of FDA's intramural research programmes and ensure that this intramural research does not duplicate research efforts supported by the Reagan-Udall Foundation.

Critical Path Public-Private Partnerships

Section 603 adds section 566 to the FDCA, authorising the Secretary to enter into collaborative agreements, known as Critical Path Public-Private Partnerships, in order to implement the Agency's Critical Path Initiative. The purpose of these partnerships is to develop innovative collaborative projects in research, education and outreach, in order to foster medical product innovation and enhance product safety. Eligible entities are limited to institutions of higher education and tax-exempt organisations described in section 501(c)(3) of the Internal Revenue Code.

Title VII: Conflicts of Interest

Section 701 of the FDAAA repeals section 505(n)(4) of the FDCA, which governs conflicts of interest on committees that

45) *Ibid.*, section 505A(l).

46) *Ibid.*, section 505A(n).

47) PHSA section 409(a).

48) *Ibid.*, section 409(b).

49) *Ibid.*, section 409(c).

provide FDA with advice regarding clinical trials of drugs and approval of new drug applications ('NDAs') and biologics licence applications ('BLAs'). It adds a new section 712 to the FDCA, which will govern management of conflicts of interest on FDA advisory committees. Title VII does not repeal or amend 18 USC section 208, which governs federal employee conflicts of interest more broadly and also applies to FDA advisory committee members. The amendments made by section 701 of the FDAAA took effect on 1 October 2007.

Recruitment and Appointments

The Secretary must engage in recruitment activities in order to recruit individuals to serve as advisory committee members.⁵⁰ These activities must include seeking input from professional medical and scientific societies to determine the most effective informational and recruitment activities.

When considering a term appointment to an advisory committee, the Secretary must review the expertise of the candidate and the financial disclosures made by that candidate pursuant to the Ethics in Government Act of 1978, in order to reduce the likelihood that an appointed individual will later have a conflict of interest.⁵¹

Disclosures, Prohibition and Waivers

Prior to every meeting of an advisory committee regarding a particular matter (as that phrase is used in 18 USC section 208), each member of the committee who is a full-time government employee or a special government employee must disclose to the Secretary all financial interests in accordance with 18 USC section 208(b).⁵² No member of an advisory committee may participate with respect to a particular matter before the committee if the member (or an immediate family member of that member) has a financial interest that could be affected by the advice given to the Secretary with respect to that matter.⁵³ The Secretary may waive this prohibition, if necessary to afford the advisory committee essential expertise, to permit a member to participate as either a voting member or a non-voting member.⁵⁴ The Secretary is to determine the percentage of 'exceptions' in fiscal year 2007 – defined as waivers under FDCA section 505(n)(4) as in effect on the day before enactment of the FDAAA, determinations under 18 USC

section 208(b), and certifications under 18 USC section 208(b)(3) – as a percentage of meeting slots.⁵⁵ The number of exceptions in fiscal year 2008 cannot exceed 95 per cent of this base percentage, and the number must decrease each year until it reaches 75 per cent in fiscal year 2012.

No later than 15 days prior to an advisory committee meeting for which the Secretary has made an exception, the Secretary must disclose on the FDA website the type, nature, and magnitude of the financial interests of any member to whom such an exception applies, as well as the Secretary's reasons for the determination, certification, or waiver.⁵⁶ If a financial interest becomes known to the Secretary less than 30 days prior to the meeting, the Secretary must make these disclosures as soon as practicable after the exception is made, but in no event later than the date of the meeting.⁵⁷ The obligation to disclose applies notwithstanding section 107(a)(2) of the Ethics in Government Act, but the Secretary is not required to disclose information protected by an exemption from FOIA or by the Privacy Act. The Secretary must ensure that the public record and transcript of every advisory committee meeting include any such disclosures.⁵⁸

Title VIII: Clinical Trial Databases

Prior to enactment of the FDAAA, section 402(i) of the PHSA required the registration, in a data bank established by NIH, of clinical trials for drugs intended for the treatment of serious or life-threatening diseases or conditions. Title VIII of the FDAAA adds section 402(j), which requires expansion of the existing data bank to include registration of medical device clinical trials and additional drug clinical trials and inclusion of clinical trial results.

Registry Data Bank

The registry data bank must be expanded to include all 'applicable' drug and device clinical trials. An 'applicable drug clinical trial' means a controlled clinical investigation, other than a phase 1 investigation, of a new drug or a biological product that is a drug.⁵⁹ An 'applicable device clinical trial' means a prospective clinical study of health outcomes in human subjects, comparing an intervention with a medical device against a control, or pediatric postmarket surveillance required under FDCA section 522.⁶⁰ The registry data bank need not include limited studies that gather essential

50) FDCA section 712(b)(1).

51) *Ibid.*, section 712(b)(2).

52) *Ibid.*, section 712(c)(1).

53) *Ibid.*, section 712(c)(2)(A).

54) *Ibid.*, section 712(c)(2)(B).

55) *Ibid.*, section 712(c)(2)(C).

56) *Ibid.*, section 712(c)(3)(A).

57) *Ibid.*, section 712(c)(3)(B).

58) *Ibid.*, section 712(d).

59) PHSA section 402(j)(1)(iii)(I).

60) *Ibid.*, section 402(j)(1)(ii).

information used to refine devices or design pivotal trials and that are not intended to determine safety and effectiveness of devices.

The Director of NIH must expand the registry data bank to include certain descriptive information, recruiting information, location and contact information, and administrative data for each covered trial.⁶¹ The descriptive information consists of a brief title and summary intended for the lay public, the primary purpose, the study design, the study phase, the study type, the primary disease or condition being studied (or the focus of the study), the intervention name and type, the study start date, the expected completion date, the target number of subjects, and the outcomes (including the primary and secondary outcome measures). The recruitment information consists of the eligibility criteria for the trial, the trial and site recruitment status, and whether there is expanded access for those who do not qualify for enrolment in the trial. The administrative data consist of the unique protocol identification number, any other protocol identification number, and FDA's IND or investigational device exemption ('IDE') number. The Secretary may, by regulation, modify these information requirements, if he or she provides a rationale for 'why the modification improves and does not reduce' the clinical trial information.

This information must be submitted for any applicable clinical trial that is initiated after the date of enactment of the FDAAA (27 September 2007), or ongoing on the date that is 90 days after the date of enactment (26 December 2007). The responsible party, defined as the clinical trial's sponsor or its principal investigator, if so designated, must submit the information to NIH by the later of: (1) 26 December 2007, or (2) 21 days after the first patient is enrolled in the clinical trial.⁶² If the trial relates to a condition that is not serious or life threatening, and if the trial was ongoing on 27 September 2007, the information is instead due on 28 September 2008.

The Director of NIH must ensure that information submitted for applicable clinical trials for devices previously approved under section 515 or section 520(m) of the FDCA or cleared under FDCA section 510(k), and applicable clinical trials for drugs, are posted to the registry data bank no later than 30 days after its submission.⁶³ For applicable clinical trials for devices not previously cleared or approved, the information must be posted in the registry no later than 30 days after the date of clearance or approval, but no earlier than the date of clearance or approval.⁶⁴ Further, the Director must ensure that the public can search entries in the registry data bank by

keyword, as well as by certain criteria such as the disease or condition being studied. Within 18 months of enactment, the Director must ensure that the public can search the registry data bank by the safety issue, if any, that is being studied.⁶⁵

The responsible party must submit updates at least once every 12 months to reflect changes to the information in the clinical trial registry, unless there were no changes to the information during that time.⁶⁶ The Director must make these updates publicly available in the registry.

Linking Registry Data Bank to Clinical Trial Results

By 26 December 2007, the Secretary must ensure that the registry data bank includes links to the following basic results information for all clinical trials that form the primary basis of an efficacy claim or are conducted after approval or clearance of the product: (1) for an applicable trial considered by an advisory committee, any posted FDA summary document regarding the trial; (2) any FDA assessment of the results of a pediatric drug trial posted in accordance with the PREA or BPCA; (3) any FDA public health advisories regarding the drug or device that is the subject of the trial; (4) in the case of a drug, the FDA action package for approval document; (5) in the case of a device, the detailed summary of information regarding its safety and effectiveness included in the PMA or the summary of safety and effectiveness data included in the 510(k) notification; (6) Medline citations to any publications focused on the results of the trial; and (7) if available, the entry for the drug in the National Library of Medicine database of structured product labels.

By 27 September 2008, the Secretary must expand the registry data bank to include additional information regarding clinical trial results for approved drugs and approved or cleared devices. This additional information must consist of: (1) a table of the demographic and baseline data collected for the trial overall and each arm of the trial to describe the study participants and drop outs; (2) the primary and secondary outcome measures, with the results of tests showing the statistical significance of the measures; (3) a point of contact for scientific information on the trial; and (4) whether there exists an agreement limiting the rights of the principal investigator to publish or discuss the results of the trial.

By 27 March 2009, the Secretary must, by regulation, determine the best method for including in the data bank information on serious and frequent adverse events for a

61) *Ibid.*, section 402(j)(2)(A).

62) *Ibid.*, section 402(j)(2)(C).

63) *Ibid.*, section 402(j)(2)(D)(i), (ii)(I).

64) *Ibid.*, section 402(j)(2)(D)(ii)(I).

65) *Ibid.*, section 402(j)(2)(B).

66) *Ibid.*, section 402(j)(4)(C).

drug. Default rules will apply if no regulation is finalised by 27 September 2009.

By 27 September 2010, the Secretary must, by regulation, further expand the registry data bank to include – for all approved products – a technical and non-technical summary of each applicable trial and its results (unless the Secretary determines that these summaries cannot be included without being misleading or promotional), along with the full protocol (or the information on the protocol that is necessary to help evaluate the results) and other information that the Secretary determines to be ‘appropriate’. The Secretary must also consider whether to extend these requirements to clinical trials for unapproved products.

In general, the responsible party for an applicable clinical trial must submit the basic results information within one year after the earlier of the estimated completion date or the actual completion date. There is a potential for extensions for ‘good cause’, and the Secretary may, by regulation, increase this deadline to 18 months. The Director of NIH must ensure that results of clinical trials are posted in the data bank no later than 30 days after they are submitted.

Additional Submissions

The new law also contains provisions relating to voluntary submissions to the data bank, as well as the Secretary’s authority to compel submissions with respect to clinical trials that are not ‘applicable’ trials and that were completed on or after 27 September 1997.⁶⁷

Enforcement

A new drug or biologics license applicant must certify, when it submits its application, that all applicable requirements of section 402(j) have been met.⁶⁸ HHS agencies may not release funds under research grants to grantees who have not complied with the submission requirements of section 402(j).⁶⁹ If an applicable clinical trial is funded in whole or in part by a grant from HHS, any grant or progress report forms required under the grant must include a certification that the sponsor has made all submissions to NIH required under section 402(j).

Failure to submit required clinical trial information and submission of false or misleading information is a prohibited act and subject to civil monetary penalties under the FDCA. Public notice of violations will also be posted.

Pre-emption and Rule of Construction

Section 801(d) of the FDAAA states that upon the expansion of the registry and results data bank by regulation, no state or local government may establish or continue in effect any requirement for the registration of clinical trials or for the inclusion of information relating to the results of clinical trials in a database. It also states that the fact of submission of clinical trial information relating to an unapproved use of a drug, if submitted in compliance with PHSA section 402(j), may not be construed by the Secretary or in any administrative or judicial proceeding as evidence of a new intended use of the drug, or as labelling or misbranding of the drug.

Title IX: Enhanced Authorities Regarding Postmarket Safety of Drugs

Subtitle A: Postmarket Studies and Surveillance

Section 901 of the FDAAA adds a new section 505(o) to the FDCA, which gives the Secretary the authority to mandate postmarket studies and clinical trials as well as postmarket labelling changes. Section 901 also adds sections 505(p) and 505-1, which govern risk evaluation and mitigation strategies (REMS).

Postmarket Studies and Clinical Trials

Section 505(o) of the FDCA authorises the Secretary to require any person that holds an approved NDA for a prescription drug or a BLA for a biological product that is a drug, and any person with such an application pending, to conduct a postmarket study or clinical trial.⁷⁰ A study or trial may be required to assess a known serious risk related to use of the drug, to assess signals of serious risk related to use of the drug, or to identify an unexpected serious risk when available data indicate the potential for a serious risk.⁷¹

The Secretary may not require a postmarket study, however, unless he or she determines that ordinary pharmacovigilance reports under section 505(k)(1) and the new active postmarket risk identification and analysis system under section 505(k)(3) will not be sufficient to accomplish these goals. In addition, the Secretary may not require a postmarket clinical trial unless postmarket studies will be insufficient to meet these goals.⁷²

⁶⁷ *Ibid.*, section 402(j)(4).

⁶⁸ *Ibid.*, section 402(j)(5)(B).

⁶⁹ *Ibid.*, section 402(j)(5)(A).

⁷⁰ FDCA section 505(o)(3)(A).

⁷¹ *Ibid.*, section 505(o)(3)(B).

⁷² *Ibid.*, section 505(o)(3)(D).

The responsible person must submit a timeline for completion of each study or trial required under section 505(o), as well as periodic reports to the Secretary on the status of the study or trial in question.⁷³ Failure to comply with the timeline or to submit the periodic reports is a violation of section 505(o), unless the responsible person demonstrates ‘good cause’ for the non-compliance.⁷⁴

Safety Labelling Changes

Section 505(o) also requires the Secretary promptly to notify responsible persons if he or she becomes aware of new safety information that should be included in the drug’s labelling.⁷⁵ Following this notification, the responsible person must either (a) submit a supplement proposing changes to the labelling to reflect the new safety information, or (b) notify the Secretary that the responsible person does not believe that a labelling change is necessary and explain the reasons for this conclusion. The Secretary must act promptly on any supplement submitted. If the Secretary disagrees with the proposed labelling changes (or with the conclusion that no change is necessary), the Secretary must initiate discussions to reach agreement on whether and how the labelling should be modified to reflect the new safety information.

At the conclusion of these discussions, the Secretary may order the responsible person to make the labelling changes the Secretary deems appropriate to address the new safety information. If the responsible person does not comply with the order by the statutory deadline, and if there is no appeal or dispute resolution proceeding pending at that time, the responsible person will be considered in violation of section 505(o).

The paragraph on safety labelling changes includes a ‘rule of construction’ that the paragraph may not be construed to affect the responsibility of an NDA holder to ‘maintain its label in accordance with existing requirements’, including 21 CFR section 314.70, which governs changes to an approved application.

REMS

Under FDCA section 505-1(a), a new drug applicant (including a person submitting an abbreviated new drug application) for a prescription drug and an applicant for a biological product that is a new drug must submit, as part of its application, a proposed REMS, if the Secretary determines that a REMS is necessary to ensure that the benefits of the drug outweigh its

risks. If a REMS is not required when an application is approved, the Secretary may later require submission of a REMS proposal only if he or she (1) becomes aware of new safety information, and (2) determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks. ‘New safety information’ means information about a serious risk or an unexpected serious risk associated with use of the drug that the Secretary has become aware of since the drug was approved.⁷⁶

Determinations by the Secretary regarding whether to require a REMS must be made by individuals ‘at or above the level of individuals empowered to approve a drug (such as division directors within the Center for Drug Evaluation and Research)’.⁷⁷ In addition, they are not subject to dispute resolution before the Drug Safety Oversight Board (‘DSOB’).⁷⁸

Every proposed REMS must include a timetable for submission of assessments of the strategy (at least on the dates that are 18 months after, and three years after, REMS approval).⁷⁹ It must include additional elements – a Medication Guide, patient package insert, or a plan for communication to healthcare providers – if the Secretary makes the relevant findings.⁸⁰ The Secretary may also require ‘elements to assure safe use’ of the drug, if a determination is made that they are necessary to mitigate a specific serious risk listed in the labelling.⁸¹ To mitigate that risk, the elements to assure safe use may require, among other things: (1) that healthcare providers who prescribe the drug have particular training, experience, or certification; (2) that patients be monitored; and (3) that patients be enrolled in a registry.⁸²

Following approval of a REMS, the application holder may submit an assessment of the REMS (which may include a proposal to modify it) at any time and must submit an assessment at certain other times: (1) when submitting a supplemental application for a new indication; (2) when required to do so by the REMS timetable; (3) when ordered to do so by the Secretary based on new safety or effectiveness information; and (4) in the case of a drug subject to an NDA, within 15 days of an order by the Secretary if the Secretary determines that there may be cause to withdraw approval of the NDA under section 505(e).⁸³

A REMS assessment must include: (1) with respect to any goal for existing ‘elements to assure safe use’, an assessment of the extent to which those elements are meeting the goal or

73) *Ibid.*, section 505(o)(3)(E).

74) *Ibid.*, section 505(o)(3)(G).

75) *Ibid.*, section 505(o)(4).

76) *Ibid.*, section 505-1(b)(3).

77) *Ibid.*, section 505-1(a)(4).

78) *Ibid.*, section 505-1(h)(5)(A)(i).

79) *Ibid.*, section 505-1(c)(1).

80) *Ibid.*, section 505-1(e).

81) *Ibid.*, section 505-1(f)(1).

82) *Ibid.*, section 505-1(f)(3).

83) *Ibid.*, section 505-1(g)(1), (2).

whether instead the goal or elements should be modified; (2) with respect to any postmarket study required under section 505(o) or otherwise undertaken to investigate a safety issue, the status of the study and whether any difficulties completing the study have been encountered; and (3) with respect to any postmarket clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue, the status of the trial, whether enrolment has begun, the number of participants enrolled, the estimated completion date, whether any difficulties completing the trial have been encountered, and 'registration information with respect to requirements' under sections 402(i) and 402(j) of the PHSA.⁸⁴

The Secretary must promptly review each proposed REMS and each REMS assessment. No later than 60 days after submission of a REMS assessment (or 30 days in the case of an assessment prompted by possible withdrawal of approval), the Secretary must initiate discussions with the responsible party. Unless the responsible person invokes dispute resolution, if modification of the REMS was proposed in a voluntary REMS assessment, or in an assessment required by the REMS, required by the Secretary because of new information, or required because grounds for withdrawal of the application may exist, the Secretary must describe the required REMS or modification in an order no later than 90 days after discussions began. When a REMS is proposed as part of an application, unless the responsible person invokes dispute resolution, the Secretary must describe the required REMS in the action letter on the application. Each action letter and order is to be made publicly available. An approved REMS remains in effect until the Secretary acts.⁸⁵

If a proposed REMS is submitted as part of an application for initial approval of the product in question, and if there is a dispute about the strategy, the applicant must use the major dispute resolution procedures set forth in the FDA's user fee reauthorisation goals letter. In all other cases, a dispute about the REMS must be handled under the dispute resolution process described in section 505-1 of the FDCA. This process is subject to strict statutory deadlines and includes a hearing before the DSOB and public disclosure of the associated transcript, with redactions to protect trade secrets and other confidential information.

A drug with an approved Abbreviated New Drug Application (ANDA) is subject to any MedGuide, patient package insert, and 'elements to assure safe use' required in the REMS of the innovator drug. The generic and innovator drugs must use a 'single, shared system' for the latter, unless the Secretary has waived this requirement. The holder of an approved NDA may

not 'use' an element to assure safe use to 'block or delay' approval of an ANDA or application under section 505(b)(2).

Section 505(o)(1) of the FDCA states that a responsible person may not introduce a new drug into commerce if the person is in violation of section 505(o)(3) or section 505(o)(4), which relate to postmarket studies, postmarket clinical trials, and safety labelling changes. Section 505(p) states that a person may not introduce into commerce a new drug that is a prescription drug, or a biological product that is a drug, if a REMS is required and the person fails to maintain compliance with the REMS or other requirements of section 505-1. In addition, failure to conduct a postmarket study required under section 506 (fast track) or FDA's subpart H (drug) and E (biologic) regulations is deemed a violation of section 505(p)(1). Further, a drug will be deemed misbranded under section 502 of the FDCA if (1) it is subject to an approved REMS and the responsible person fails to comply with a requirement of the REMS, or (2) the responsible person violates a requirement of section 505(o)(3) (relating to postmarket studies and trials) or section 505(o)(4) (relating to safety labelling changes). Finally, a responsible person who violates a requirement of section 505(o), section 505(p), or section 505-1 is subject to a civil money penalty under a new section 303(f)(4) of the FDCA.

Prescription Drug Advertising

Section 901 of the FDAAA also adds a new section 503B to the FDCA. Under section 503B, the Secretary may require the submission, for review, of any television advertisement for a drug no later than 45 days before dissemination of the advertisement.⁸⁶ The Agency may not collect DTC user fees with respect to a submission mandated under this section. In conducting a review under this section, the Secretary may make recommendations, with respect to 'information included in the label of the drug', on changes that are necessary to protect 'the consumer good and well-being' or changes that are 'consistent with prescribing information for the product'. In addition, he or she may make recommendations with respect to 'information included in the label of the drug', if appropriate and if information exists, on statements for inclusion in the advertisement 'to address the specific efficacy of the drug as it relates to specific population groups', such as the elderly, children, and racial and ethnic minorities.⁸⁷ The preceding provisions do not authorise the Secretary to make or direct changes in the material submitted. Section 503B does, however, authorise the Secretary to require disclosure of a specific risk in the labelling and disclosure of the product's date of approval, in certain situations.⁸⁸

⁸⁴ *Ibid.*, section 505-1(g)(3).

⁸⁵ *Ibid.*, section 505-1(h).

⁸⁶ *Ibid.*, section 503B(a).

⁸⁷ *Ibid.*, section 503B(b).

⁸⁸ *Ibid.*, section 503B(e).

Section 901 also amends section 502(n) of the FDCA to mandate that in the case of a DTC television or radio advertisement for a prescription drug, if the advertisement states the name of the drug and its conditions of use, the ‘major statement’ relating to side effects and contra-indications must be presented in a ‘clear, conspicuous, and neutral manner’. Section 901 also directs the Secretary, within 30 months of enactment of the FDAAA to, ‘by regulation establish standards for determining’ whether the major statement is presented in the manner required. And it deletes the provision in section 502(n) that requires prescription drug advertising regulations to be developed through formal section 701(e) rule-making procedures.

Dissemination of a television advertisement without complying with section 503B is a new prohibited act.⁸⁹ Section 901 also amends section 303 of the FDCA to create a new civil money penalty provision tied to DTC advertising.⁹⁰

Active Postmarket Risk Identification and Analysis System

Section 905 of the FDAAA adds paragraphs (3) and (4) to section 505(k) of the FDCA, requiring the Secretary to establish an active postmarket risk identification and analysis system.

Under paragraph (3), within two years of enactment, the Secretary must develop methods to obtain access to disparate data sources (including data from the Medicare program and private sector health insurance claims data) and develop validated methods for establishment of a system to link and analyse these data, with a goal of including at least 100 million patients by July 2012. Within one year of the development of these methods, the Secretary must establish and maintain actual procedures for, among other things, risk identification and analysis based on electronic health data.

Paragraph (4) requires ‘advanced’ analysis of drug safety data and will entail, among other things, (a) establishment of a public process to identify priority drug safety questions and consider mechanisms for responding to those questions, and (b) contracting with qualified entities to allow for prompt investigation of those questions.

Effective Date; Drugs Approved Before Effective Date

Subtitle A ‘takes effect 180 days after the date of enactment of this Act’.⁹¹

Certain drugs approved ‘before the effective date of this Act’ are deemed to have, already, an approved REMS. These are drugs with ‘elements to assure safe use’ imposed under subpart H (drugs) or subpart E (biologics), and drugs with

such elements to which the applicant has otherwise agreed. The REMS in question is deemed to consist of the timetable for REMS assessment required under section 505-1(d) of the FDCA, as well as any additional elements under sections 505-1(e) (MedGuide, patient package insert, and communication plan) and 505-1(f) (elements to assure safe use) already in effect for the drug. This REMS is subject to enforcement to the same extent as any other REMS, except that the new civil money penalty and misbranding provisions do not apply before the Secretary completes his or her review of (and acts on) the first assessment of the REMS under section 505-1. Section 909 of the FDAAA states that not later than 180 days after the effective date of the FDAAA, the holder of the approved application for a drug deemed to have a REMS must submit a proposed REMS to the Secretary. That submission is subject to section 505-1 as if it had been submitted with the application in the first instance.⁹²

Subtitle B — Other Provisions to Ensure Drug Safety and Surveillance

Antibiotic Drugs

Section 911 of the FDAAA creates a new section 511 of the FDCA, requiring the Secretary to issue guidance for the conduct of clinical trials for antibiotic drugs within one year of enactment of the FDAAA. No later than five years after enactment, the Secretary must review and update the guidance to reflect developments in scientific and medical information and technology.

Prohibition against Foods to which Drugs or Biological Products have been Added

Section 912 of the FDAAA amends section 301 of the FDCA by adding a new subsection (ll). Under subsection (ll), unless an exception applies, it is a prohibited act to introduce into interstate commerce any food to which has been added a drug approved under section 505 of the FDCA, a biological product licensed under section 351 of the PHSA, or a drug or biological product for which ‘substantial clinical investigations’ have been instituted and for which the existence of such investigations has been made public.

Assuring Pharmaceutical Safety

Section 913 of the FDAAA creates a new section 505D of the FDCA, which requires the Secretary to develop standards and identify and validate technologies that can be used to secure the drug supply chain against counterfeited, diverted, subpotent, substandard, adulterated, misbranded, and expired drugs.

89) *Ibid.*, section 301(kk).

90) *Ibid.*, section 303(g)(1).

91) FDAAA section 909(a).

92) *Ibid.*, section 909(b).

Citizen Petitions

Section 914 of the FDAAA adds a new subsection (q) to section 505, regarding petitions and civil actions that relate to approval of applications submitted under section 505(j) or described in section 505(b)(2). The subsection does not apply to a petition relating solely to the timing of approval of an ANDA in light of the 180-day exclusivity provisions or to a petition filed by the ANDA applicant itself.

The Secretary may not delay approval of such an application because of any request to take action regarding that application, except in response to a citizen petition or petition for a stay of action, and only if he or she has determined that a delay is necessary to protect the public health. If the Secretary makes this determination, he or she must notify the applicant within 30 days and summarise the substantive issues raised in the petition. If the Secretary determines that the petition or a supplement to the petition was submitted with the 'primary purpose' of delaying approval of the application and that the petition does not on its face raise 'valid' scientific or regulatory issues, he or she may deny the petition at any point.

The Secretary must take 'final agency action' on a petition no later than 180 days after it was submitted and may not extend this deadline for any reason. If the generic drug application in question received first-filer status for purposes of 180-day exclusivity and approval of the application was delayed because of the petition, the 30-month deadline for tentative approval (which triggers forfeiture of exclusivity) is extended by the number of days the petition is pending. Finally, the Secretary may not consider a petition unless it is signed and contains a certification (or, in the case of a supplement or comments on a petition, a verification) regarding, among other things, sources of remuneration and the date on which the underlying information was first learned.

Postmarket Drug Safety Information for Patients and Providers

Section 915 of the FDAAA adds a new subsection (r) to section 505 of the FDCA, which requires the Secretary to improve the 'transparency' of information about drugs and to allow patients and providers better access through the internet to information about drugs. Within one year after enactment, the Secretary must establish a website that contains links to safety information for each prescription drug approved under section 505 or licensed under section 351 of the PHSA, including a link to the clinical trial data bank entries for the drug and safety information and alerts issued by FDA, including product recalls, warning letters, and import alerts.

Action Package for Approval

Section 916 of the FDAAA amends section 505(l) of the FDCA by adding paragraph (2). This new paragraph (2) requires publication on the FDA website of an 'action package for approval' of each application under section 505(b) of the FDCA or section 351 of the PHSA. Within 48 hours after approval of the application, except where redaction is required, the Secretary must publish a summary review that documents conclusions about the drug from all reviewing disciplines, noting any critical issues and disagreements with the applicant and within the review team and how they were resolved, recommendations for action, and an explanation of any non-concurrence with review conclusions. The remaining pieces of the action package must be posted within 30 days of approval, if the application relates to a drug no active ingredient (including any ester or salt of the active ingredient) of which has been previously approved in an application under section 505 of the FDCA or section 351 of the PHSA, or within 30 days of the third request under FOIA for any other drug. Those pieces include: (1) documents generated by FDA related to review of the application; (2) labelling submitted by the applicant; and (3) the Division Director and Office Director's decision document. The new paragraph does not authorise the disclosure of any trade secret, confidential commercial or financial information, or other matter protected from disclosure under FOIA.

Database for Authorized Generic Drugs

Section 920 of the FDAAA amends section 505 of the FDCA by adding a new subsection (t), which requires the Commissioner to publish, within nine months of enactment, a complete list on the FDA website of all authorised generic drugs.⁹³ This list must include each authorised generic drug included in annual reports submitted to the Secretary by the sponsor of the listed drug after 1 January 1999, and it must be updated quarterly.

Risk Communication

Section 917 of the FDAAA adds section 567 to the FDCA, requiring the Secretary to establish an Advisory Committee on Risk Communication, which will advise the Commissioner on methods to communicate effectively the risks associated with products regulated by FDA.

Referral to Advisory Committee

Section 918 of the FDAAA adds a new subsection (s) to section 505 of the FDCA. Under this subsection, if an application relates to a drug no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under section 505 or section 351 of the

93) An 'authorized generic drug' is defined to mean a listed drug that has been approved under section 505(c) of the FDCA and is marketed, sold, or distributed directly, or indirectly, to retail class of trade under labelling,

packaging (other than repackaging as the listed drug), product code, labeller code, trade name, or trade mark different from the listed drug. FDCA section 505(t)(3).

PHSA, the Secretary must either refer the drug to an advisory committee or state in the action letter on the application the reasons the Secretary did not refer the drug.

Adverse Drug Reaction Reports and Postmarket Safety

Section 921 of the FDAAA adds a paragraph (5) to section 505(k), requiring the Secretary to conduct regular screening of the Adverse Event Reporting System ('AERS') database and to post quarterly reports on the AERS website of any new safety information or potential signals of serious risk. It also requires annual review of the backlog of postmarket safety commitments to determine which should be revised or eliminated, with reporting to Congress on those determinations.

Title XI: Other Provisions

Subtitle A: In General

Scientific Articles Published by FDA Employees

Section 1101 of the FDAAA adds a new section 713 to the FDCA, requiring clear and publicly available written policies on the review and clearance of scientific articles (including papers, posters, abstracts, books, book chapters, and other published writing) published or presented by FDA employees.⁹⁴

Treatments for Tropical Diseases

Section 1102 of the FDAAA adds a new section 524 to the FDCA, which authorises the use of priority review vouchers to encourage the development of treatments for tropical diseases.

Subtitle B: Antibiotic Access and Innovation

Identification of Clinically Susceptible Concentrations of Antimicrobials

Section 1111 of the FDAAA requires the Commissioner to identify, periodically update, and post on the internet 'clinically susceptible concentrations', meaning specific values that characterise bacteria as clinically susceptible, intermediate, or resistant to a drug or drugs being tested.

Orphan Antibiotic Drugs

Section 1112 of the FDAAA requires the Commissioner to convene a public meeting regarding which serious and life-threatening infectious diseases, such as diseases due to gram-negative bacteria and other diseases due to antibiotic-resistant bacteria, potentially qualify for grants and contracts under the Orphan Drug Act.

Exclusivity of Certain Drugs Containing Single Enantiomers

Section 1113 of the FDAAA revises section 505 of the FDCA by adding a new subsection (u). Under section 505(u), the sponsor of an application under section 505(b) for a non-racemic drug containing as an active ingredient (including any ester or salt of the active ingredient) a single enantiomer of a previously approved racemic drug may elect to have the single enantiomer not considered the 'same active ingredient' as that contained in the previously approved racemic drug if certain requirements are met.⁹⁵ If an applicant makes the election, then until ten years after approval of the non-racemic drug, the Secretary may not approve the non-racemic drug for any condition of use in the therapeutic category in which the racemic drug has been approved.⁹⁶ Section 505(u) expires in fiscal year 2012.⁹⁷

94) *Ibid.*, section 713(a), (b).

95) *Ibid.*, section 505(u)(1).

96) *Ibid.*, section 505(u)(2)(A).

97) *Ibid.*, section 505(u)(4).