MedWatch: The Food and Drug Administration Medical Products Reporting Program
0910-0291
SUPPORTING STATEMENT

Terms of Clearance: none

A. Justification

1. Circumstances Making the Collection of Information Necessary

Abstract: Members of the public use FDA's MedWatch system to report adverse events, product problems, errors with the use of a human medical product, or when evidence of therapeutic failure is suspected or identified in clinical use. To ensure the marketing of safe and effective products, it is critical that postmarketing adverse outcomes and product problems are reported for all FDA-regulated human healthcare products, including drugs (prescription and nonprescription), biologics, medical devices, dietary supplements and other special nutritional products (e.g. infant formula and medical foods), and cosmetics. To facilitate reporting on human medical products (except vaccines) during their postapproval and marketed lifetimes, three forms (collectively known as the MedWatch forms) are available from the Agency. Form FDA 3500 is intended to be used for voluntary (i.e., not mandated by law or regulation) reporting by healthcare professionals. Form FDA 3500B is written in plain language and is intended to be used for voluntary reporting (i.e., not mandated by law or regulation) by consumers (i.e., patients and their caregivers). Form FDA 3500A is used for mandatory reporting (i.e., required by law or regulation).When FDA receives this information from healthcare professionals, patients, or consumers, the report becomes data that will be used to assess and evaluate the risk associated with the product. FDA will then take whatever action is necessary to reduce, mitigate, or eliminate the public's exposure to the risk through regulatory and public health interventions.

Authorizing Statutes and Codified Regulations: The Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353b, 355, 360i, 360l and 393); and the Public Health Service Act (42 U.S.C. 262) represent the statutory authority for the FDA to collect mandatory adverse event reports from regulated industry on medical products once approved for marketing - to monitor the safety of drugs, biologics, medical devices and dietary supplements. There are no laws or regulations mandating the post-market reporting for medical foods, infant formula, cosmetics or tobacco products, and the reporting for these products is done voluntarily.

Requirements regarding mandatory reporting of adverse events or product problems have been codified in parts 310, 314, 600, and 803 (21 CFR 310, 314, 600, and 803), specifically §§ 310.305, 314.80, 314.98, 600.80, 803.30, 803.50, 803.53, 803.56, and specified in sections 503B, 760, and 761 of the FD&C Act. Mandatory reporting of adverse reactions for human cells, tissues, and cellular- and tissue based products (HCT/Ps) has been codified in 21 CFR 1271.350.

USE OF FORM 3500 (Voluntary Reporting)

This voluntary version of the form may be used by healthcare professionals to submit all reports not mandated by Federal law or regulation. Individual health professionals are not required by law or regulation to submit reports to the Agency or the manufacturer with the exception of certain adverse reactions following immunization with vaccines as mandated by the National Childhood Vaccine Injury Act of 1986 (42 U.S.C. 300aa–1). Reports for vaccines are not submitted via MedWatch or MedWatch forms, but are submitted to the Vaccines Adverse Event Reporting System (see http://vaers.hhs.gov), which is jointly administered by FDA and the Centers for Disease Control and Prevention (CDC).

Hospitals are not required by Federal law or regulation to submit reports associated with drug products, biological products, or special nutritional products. However, hospitals and other user facilities are required by Federal law to report medical device-related deaths and serious injuries.

Under Federal law and regulation, section 761(b)(1) of the FD&C Act, a dietary supplement manufacturer, packer, or distributor whose name appears on the label of a dietary supplement marketed in the United States is required to submit to FDA any serious adverse event report it receives regarding use of the dietary supplement in the United States. However, FDA bears the burden to gather and review evidence that a dietary supplement may be adulterated under section 402 of the FD&C Act after that product is marketed. Therefore, the Agency depends on the voluntary reporting by health professionals, and especially by consumers, of suspected serious adverse events and product quality problems associated with the use of dietary supplements. All dietary supplement reports were previously received by the Agency on paper versions of Form FDA 3500 (or Form FDA 3500B) (by mail or fax). Currently, electronic reports may be sent to the Agency via an online submission route called the Safety Reporting Portal (http://www.safetyreporting.hhs.gov/). In that case, Form FDA 3500 (or Form FDA 3500B) is not used.

Form FDA 3500 may be used to report to the Agency serious adverse events, product problems, and product use errors and therapeutic failures. The form is provided in both paper and electronic formats. Reporters may mail or fax paper forms to the Agency (a fillable PDF version of the form is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf) or reporters may electronically submit a report via the MedWatch Online Voluntary Reporting Form (https://www.accessdata.fda.gov/scripts/medwatch/). Reporting is supported for drugs, non-vaccine biologicals, medical devices, special nutritional products, cosmetics, and non-prescription (over the counter (OTC)) human drug products marketed without an approved application. The paper form may also be used to submit reports about tobacco products and dietary supplements. Electronic reports for tobacco products and dietary supplements may be submitted to the Agency via an online submission route called the Safety Reporting Portal (http://www.safetyreporting.hhs.gov/).

USE OF FORM 3500B (CONSUMER VOLUNTARY REPORTING)
This voluntary version of the form may be used by consumers (i.e. patients and their caregivers) to submit reports not mandated by Federal law or regulation. Individual patients or their caregivers are not required by law or regulation to submit reports to the Agency or the manufacturer.

FDA supports and encourages direct reporting to the Agency by consumers of suspected serious adverse outcomes and other product problems associated with human medical products, (http://www.fda.gov/Safety/ReportaProblem/default.htm). Since the inception of the MedWatch program, launched in July 1993 by then FDA Commissioner David Kessler, the program has been promoting and facilitating voluntary reporting by both the general public and healthcare professionals. FDA has further encouraged voluntary reporting by requiring inclusion of the MedWatch toll-free phone number or the MedWatch Internet address on all outpatient drug prescriptions dispensed, as mandated by section 17 of the Best Pharmaceuticals for Children Act (Pub. L. 107–109).

On March 25, 2008, section 906 of the Food and Drug Administration Amendments Act (Pub. L. 110–85) amended section 502(n) of the FD&C Act and mandated that published direct-to-consumer advertisements for prescription drugs include the following statement printed in conspicuous text (this includes vaccine products): ‘‘You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/safety/medwatch, or call 1–800–FDA–1088.’’

Most private vendors of consumer medication information, the drug product-specific instructions dispensed to consumers at outpatient pharmacies, remind patients to report ‘‘side effects’’ to FDA and provide contact information to permit reporting via the MedWatch process.

Since 2013, FDA has made available Form FDA 3500B. It was proposed during the previous authorization in 2012 and is a version of Form FDA 3500 that is tailored for consumers and written in plain language (in conformance with the Plain Writing Act of 2010 (Pub. L. 111–274) http://www.gpo.gov/fdsys/pkg/PLAW-111publ274/pdf/PLAW-111publ274.pdf).

Form FDA 3500B evolved from several iterations of draft versions, with input from human factors experts, from other regulatory agencies, and with extensive input from consumer advocacy groups and the general public. Form FDA 3500B may be used to report to the Agency adverse events, product problems, and product use errors. The form is provided in both paper and electronic formats. Reporters may mail or fax paper forms to the Agency (a fillable PDF version of the form is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM349464.pdf) or electronically submit a report via the MedWatch Online Voluntary Reporting Form (https://www.accessdata.fda.gov/scripts/medwatch/). Reporting is supported for drugs, non-vaccine biologicals, medical devices, special nutritional products, cosmetics, and non-

prescription OTC human drug products marketed without an approved application. The paper form may also be used to submit reports about tobacco products and dietary supplements. Electronic reports for tobacco products and dietary supplements may be submitted to the Agency via an online submission route called the Safety Reporting Portal (http://www.safety reporting.hhs.gov/).

USE OF FORM FDA 3500A [MANDATORY VERSION]

A. Drug and biological products

In sections 505(b), 505(j), 503B, and 704 (21 U.S.C. 374) of the FD&C Act, Congress has required that important safety information relating to all human drug products be made available to the FDA so that it can take appropriate action to protect the public health when necessary. Section 702 of the FD&C Act (21 U.S.C. 372) authorizes investigational powers to the FDA for enforcement of the FD&C Act. These statutory requirements regarding mandatory reporting have been codified by FDA under parts 310 and 314 (drugs) and 600 (biological products). Mandatory reporting of adverse reactions for HCT/Ps has been codified in 21 CFR 1271.350.

B. OTC monograph drug products and dietary supplements

Section 760 of the FD&C Act (21 U.S.C. 379aa) provides for mandatory safety reporting for non-prescription human drug products marketed without an approved application as described in the Dietary Supplement and Nonprescription Drug Consumer Protection Act (Pub. L. 109–462, December 22, 2006), which became law on December 22, 2006. The law requires manufacturers, packers, and distributors of nonprescription, over-the-counter (OTC) human drug products marketed without an approved application (OTC monograph drug products) to submit reports of adverse experiences from domestic sources. The law also requires reports of serious adverse events to be submitted to FDA by manufacturers of dietary supplements.

C. Postmarketing Safety Reports—Changes in Format Starting in June 2015

Current requirements specify that postmarketing adverse experience reports must be submitted on paper on Form FDA Form 3500A (or the CIOMS (Council for International Organizations of Medical Sciences) I form for serious, unexpected adverse experiences from a foreign source). For the last several years the Agency has accepted electronic submissions in lieu of the paper Form FDA 3500A on the condition they are submitted in a manner that the Agency can process, review, and archive. On June 10, 2014, the Agency issued a final rule entitled ‘‘Postmarketing Safety Reports for Human Drug and Biological Products; Electronic Submission Requirements’’ (79 FR 33072) that requires electronic submission of all mandatory postmarketing safety reports, including individual case safety reports. Entities with mandatory reporting obligations under parts 310 and 314 (drugs) and 600 (biological products) and specified under section 760 of the FD&C Act must implement this rule within 1 year of the issuance date (by June 10, 2015). For more information see: http://www.gpo.gov/fdsys/pkg/FR-2014-06-10/pdf/2014-13480.pdf.

B. Medical device products

Section 519 of the FD&C Act (21 U.S.C. 360i) requires manufacturers and importers of devices intended for human use to establish and maintain records, make reports, and provide information, as the Secretary of Health and Human Services may, by regulation, reasonably be required to provide assurance that such devices are not adulterated or misbranded and to otherwise assure its safety and effectiveness. The Safe Medical Devices Act of 1990 (Pub. L. 101–629), signed into law on November 28, 1990, amends section 519 of the FD&C Act. The amendment requires that user facilities such as hospitals, nursing homes, ambulatory surgical facilities, and outpatient treatment facilities report deaths related to medical devices to FDA and to the manufacturer, if known. Serious illnesses and injuries are to be reported to the manufacturer or to FDA if the manufacturer is not known. These statutory requirements regarding mandatory reporting have been codified by FDA under 21 CFR part 803 (part 803). Part 803 mandates the use of Form FDA 3500A for reporting to FDA on medical devices. The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) (Pub. L. 107–250), signed into law October 26, 2002, amended section 519 of the FD&C Act. The MDUFMA amendment (section 303) required FDA to revise the MedWatch forms to facilitate the reporting of information relating to reprocessed single-use devices, including the name of the reprocessor and whether the device has been reused.

2. <u>Purpose and Use of the Information Collection</u>

To implement these provisions for reporting on human medical products during their post-approval and marketed lifetimes, three forms are available from the Agency.

Form FDA 3500 is used for voluntary (i.e., not mandated by law or regulation) reporting by healthcare professionals. Form FDA 3500B is a consumer-friendly version of Form FDA 3500 that is intended for use by the general public who are not healthcare professionals (i.e. patients, caregivers).

Form FDA 3500A is used for mandatory reporting (i.e., required by law or regulation), primarily by regulated industry reporters but also for certain User Facility reporters for medical device-related deaths and serious injuries.

Respondents to this collection of information are both individuals and the private sector entities. Individual (voluntary) respondents include healthcare professionals, medical care organizations and other user-facilities (e.g. extended care facilities, ambulatory surgical centers), and consumers (i.e., patients and caregivers). Private sector respondents include manufacturers of biological, dietary supplement and drug products or medical devices, and importers.

Information received by FDA from either the voluntary Form FDA 3500 and Form FDA 3500B or from the mandatory Form FDA 3500A is entered into one of several databases for review by the postmarket safety surveillance staff within the individual FDA Centers that regulate human

medical products and food [Drugs, Biologics, Medical Devices, Special Nutritional Products, Cosmetics, and Tobacco]. The information in these reports may identify a previously unknown signal, suggesting an adverse outcome, unexpected harm or risk associated with a specific human medical product or class of products, identify a product use error (or "near miss") with use of a drug or medical device, or a suspected therapeutic failure or therapeutic inequivalence between drug products of known bioequivalence.

In most cases, Agency regulatory actions to reduce or eliminate the public's exposure to these medical product risks are not taken on a single case report but are dependent on aggregate analysis of trends in reports to signal potential problems that require further epidemiological investigation. Reports that may at first appear relatively insignificant may be forerunners of the development of more serious conditions (e.g., reports of pancytopenia early in the marketing of a drug may herald later reports of life-threatening aplastic anemia). Therefore, reports received early in the marketed life of a product may play a role in determining the need for later regulatory action.

After identifying a suspected new risk based on receipt of these voluntary or mandatory reports, the Agency can take the next steps in the Risk Management process including: 1) risk evaluation, using this same information supplemented by additional data sources such as postmarket studies with safety outcomes, adverse event reports from other countries, FDA's Sentinel surveillance system, or information from adverse event surveillance in other countries, 2) when indicated, will develop a risk intervention or mitigation plan to modify use of the product to reduce the potential for harm , and 3) a risk communication strategy to share the new management steps with both the general public, and those healthcare professionals and their organizations who serve the public.

The FDA's MedWatch program issues over 180 safety alerts annually and from 30-60 drug safety labeling changes each month to inform the health care community and the U.S. public of newly discovered safety information for all human medical products. See http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm433045.htm for a recent example of safety-related drug labeling changes. Many of these actions start with an initial report from a health professional or patient, whether directly to FDA or indirectly to the manufacturer and then to FDA. All new safety information is posted on the Internet, as it becomes available (see, for example, http://www.fda.gov/Safety/MedWatch/default.htm). Notifications of new postings are also sent out via e-mail notification to over 300,000 individual recipients and RSS feeds to both individual providers and patients and to over 100 MedWatch Partner organizations.

3. Use of Improved Information Technology and Burden Reduction

Use of Improved Information Technology: There are no technical or legal obstacles to the use of improved information technology to reduce the burden of reporting the information.

Voluntary Reporting: Reporting by consumers and health professionals directly to the FDA is voluntary. To facilitate such reporting, the Agency has two toll free numbers available. The number 1-800-FDA-1088 may be used to report by phone, to request forms and information on reporting, or to have a blank form faxed or mailed to the potential reporter. The number 1-800-FDA-0178 is used for faxing completed forms to the Agency.

Since 1997, both consumers and healthcare professionals have been offered an opportunity to use one of several web-based versions of Form FDA 3500. The online version of the format, www.fda.gov/medwatch/report.htm, was revised and updated in 2013 to allow for the introduction of the consumer-friendly 3500B and to make the online reporting tool mobile-friendly so that consumers and healthcare professionals could submit reports using a tablet or smartphone.

These electronic reports are triaged to the appropriate Center for review and evaluation. In addition, FDA has provided fillable PDF versions of forms FDA 3500, 3500A, and 3500B with instruction and help buttons imbedded, in order to facilitate completion of the forms.

All dietary supplement reports were originally received by the Agency on paper versions of the voluntary reporting Form 3500 (by mail or FAX). Today, electronic reports may be sent to the agency via an online submission route called the Safety Reporting Portal (http://www.safetyreporting.hhs.gov/), which is captured under OMB control number 0910-0645. In that case the Form FDA 3500 is not used.

Similarly, voluntary reporting of Tobacco products may be completed electronically online using the safety reporting portal (refer to 0910-0645 SSA 2013). Voluntary reporters who find it too difficult to submit tobacco reports using the electronic system will be able to provide their information by telephone, or, by completing the paper MedWatch form and submitting it by mail or FAX.

Mandatory Reporting:

Current CDER/CBER requirements specify that mandatory postmarket adverse experience reports must be submitted on paper on FDA Form 3500A (or the CIOMS I form for serious, unexpected adverse experiences from a foreign source), but for the last several years the Agency has accepted electronic submissions in lieu of the paper FDA Form 3500A on the condition they are submitted in a manner that the Agency can process, review, and archive. On June 10, 2014, the Agency issued a final rule entitled Postmarketing Safety Reports for Human Drug and Biological Products; Electronic Submission Requirements (79 FR 33072) that requires electronic submission of all mandatory postmarket safety reports, including individual case safety reports. Entities with mandatory reporting obligations must implement this rule within one year of the issuance date (by June 10, 2015). For more information see: http://www.gpo.gov/fdsys/pkg/FR-2014-06-10/pdf/2014-13480.pdf.

In 2014 approximately 8% of the total reports received were submitted via the Medwatch 3500, 3500A, 3500B forms, and approximately 92% of mandatory reports submitted to the FAERS database for drugs and biologicals were submitted electronically via an electronic gateway with standardized medical terminology, standardized data elements and electronic transmission standards as recommended by International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human

Use in the M1 (International Medical Terminology), M2 (Electronic Standards for the Transfer of Regulatory Information), and E2B (Data Elements For Transmission of Individual Case Safety Reports) initiatives. After the electronic submission requirements rule is in effect on June 10, 2015, the FDA will no longer accept mandatory postmarketing safety reports on paper. All such reports will be required to be submitted electronically.

Medical Device Reporting: Electronic Submission Requirements: Final Rule which takes effect on Aug 14, 2015. Manufacturers must submit initial and supplemental reports to FDA in an electronic format that FDA can process, review, and archive. Importers must also submit initial reports to FDA in an electronic format. User facilities will continue to submit reports to FDA and the manufacturer in a paper format on FDA Form 3500A. Currently FDA estimates that 72% of reports are submitted electronically. FDA estimates that after the medical device reporting electronic submission requirements are enacted the volume of paper-based mandatory medical device reports from manufacturers and importers will be significantly reduced.

All mandatory dietary supplement reports were originally received by the Agency on paper versions of the mandatory Form 3500A. Today, electronic reports may be sent to the agency via an online submission route called the Safety Reporting Portal (http://www.safetyreporting.hhs.gov/), which is captured under OMB control number 0910-0645. In that case the paper-version of Form FDA 3500A is not used.

4. Efforts to Identify Duplication and Use of Similar Information

The necessary information on serious, unexpected and unknown adverse events and product quality problems for all regulated medical products that is used on a daily basis by FDA to conduct its postmarket human medical product safety surveillance is not available from any other source.

Use of Form FDA 3500A, Form FDA 3500, and Form FDA 3500B as well as the electronic submission of the individual case reports as described above are means by which FDA obtains the information needed to monitor the safety of marketed medications, medical devices and other FDA-regulated products. The information collected using the MedWatch reporting forms FDA 3500 and 3500B are individual reports of single, unique events experienced by a patient and/or observed by a healthcare professional. These unique events are then submitted either directly to the FDA or indirectly to the manufacturer or other mandatory reporter and then to FDA.

Similar existing formation on suspected adverse events and product quality problems are collected by accreditation agencies, patient safety organizations, industry trade groups, and regulatory agencies of other nations, and while summary data may be shared or published, and while the Agency communicates regularly with these organizations and foreign regulatory bodies to discuss safety signals of concern, there is not usually direct access to these data sources. Furthermore foreign data is not sufficiently 'similar' to data on U.S. products to serve as a substitute source.

5. Impact on Small Businesses or Other Small Entities

The information being requested from voluntary reporters on Form FDA 3500 or Form FDA 3500B or required of mandatory reporters on Form FDA 3500A has been held to the absolute minimum required for the intended use of the data. The data collected in each form is essentially the content requested in 1993 when the two forms were created. This data has been modified or supplemented only based on requirements secondary to new federal law and the final published rules and regulations that were implemented to carry out those mandates. FDA believes that its duty requires the equal application of the regulations to all enterprises. While FDA does not believe it can apply different standards with respect to statutory requirements, the Agency does provide special help to small businesses (e.g. through the CDER Small Business and Industry Assistance program http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/)

6. Consequences of Collecting the Information Less Frequently

Voluntary reporting is done by consumers/patients and their healthcare professionals on an ad hoc basis and not at any suggested or required frequency. FDA encourages voluntary reporters to identify and report suspected serious adverse events in a timely fashion after experiencing or observing the event. Less frequent data collection would delay identification of products responsible for adverse reactions, including fatalities and permanent injuries. Appropriate FDA action, such as changes in labeling, implementation of a Risk Evaluation and Mitigation Strategy (REMS) or product corrections and withdrawal from the market, would be delayed by less frequent reporting.

For mandatory reporting of drug and biological products, the frequency of reporting is stratified based on the seriousness and unexpectedness of the adverse experience as defined in regulations. Reports of serious adverse experiences that are not listed in the product's current labeling must be reported within 15 calendar days of the initial receipt of the information by the applicant. Non-serious adverse experiences or serious adverse experiences that are included in the product's current labeling must be reported no later than the due date of the periodic safety report, which is submitted either quarterly or annually. For HCT/Ps, certain serious adverse reactions are required to be reported within 15-days if the manufacturer determines there is a reasonable possibility that the HCTP caused the reaction. Rapid reporting is necessary for such reports because evaluation and possible intervention to prevent any additional infectious transmission may be required. To reduce reporting burden for HCT/Ps, non-serious events or events where there is not a reasonable possibility that the HCT/P caused the reaction are not required to be reported.

For medical devices, reports of deaths, serious injuries and malfunctions are normally received within a 30 day time frame, regardless of whether the event is expected or unexpected. If during the investigation of these adverse events, a determination is made by the company or by FDA that remedial action is needed to prevent an unreasonable risk of substantial harm to public health, the reports are required to be submitted within 5 days.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

Mandatory reporters using Form FDA 3500A are required by regulation to report certain serious and unexpected adverse experiences associated with drugs, biological products, and medical devices within a specified time interval after the reporting entity learns about the report from either the patient or healthcare professional. Except for that circumstance necessary to avoid delay in FDA's learning of and evaluating the safety of a drug or device and implementing mitigating actions, there are no other special circumstances for this collection of information.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

8a. Publication in the FEDERAL REGISTER

In accordance with 5 CFR 1320.8(d), FDA published a 60 day notice for public comment in the FEDERAL REGISTER of 12/11/2014 (79 FR 73591). Four comments were received.

MedWatch 60-day Federal Register Notice – Response to Comments

A. **Comments affecting all three forms (3500, 3500A, 3500B)**

Comment – One commenter recommended the option of an "unknown" check box for race/ethnicity.

FDA Response – FDA disagrees with this comment as it is inconsistent with the OMB standards for the classification of federal data on race and ethnicity.

Comment – One commenter requested an implementation date of 18 months after publication of the finalized form.

FDA Response - FDA will allow sufficient time for implementation.

B. **Comments affecting FDA Form 3500 and FDA Form 3500A**

Comment: Section G Field 4 and Section C Field 6 We propose to add a third checkbox labeled "unknown" for when this type of information is not received. Rationale: This information may not be received.

FDA Response: FDA disagrees. G4 corresponds to "Date Received by Manufacturer" on Form 3500A. This is a required element and the manufacturer should always have this information. C6 corresponds to Lot # on the existing form 3500A. If this information is unknown the field should be left blank.

Comment: In Section A1: Along with Patient Identifier, in bracket (first, last) can be added for better identification.

FDA Response - FDA disagrees. Capturing this data may discourage people from submitting voluntary reports. The instructions for the form state “Do not use the patient's name or social security number.”

Comment: In Section A2, Age group can be added.

FDA Response - FDA disagrees. The WG believes that the two data elements proposed for age – Age with checkboxes for days, weeks, months, years, and date of birth in the format DD-MMM-YYYY are sufficient to capture this data.

Comment: In Section A3, after selecting Female, a check box should populate for pregnancy with options Yes, No, UNK. Pregnancy can be removed from section B7.

FDA Response - FDA disagrees. The agency believes pregnancy status is captured sufficiently well through existing field B7.

Comment: In Section B1, if Product problem check box is selected then only a text box to enter NDC# should come as National drug code is required ONLY when reporting a drug product problem. It can be removed from C9.

FDA Response - FDA disagrees. Product problem is not limited to drug products, and may include medical devices, biologics and other products which would not have an associated NDC number.

Comment: 5. In section B2, Hospitalization - initial or prolonged can be relabeled to only Hospitalization and can have three check boxes; Initial, Prolonged and Hospital discharge summary available. Reporter can select whichever is applicable.

FDA Response - FDA Disagrees. We encourage reporters to put more detail about the hospitalization in the narrative text.

Comment: In section B5, Describe Event or Problem, along with individual event terms, seriousness criteria for each event should be populated, so that event wise seriousness criteria can be identified.

FDA Response - FDA disagrees. An event is considered serious if it meets the regulatory definition, as outlined code of federal regulations 21CFR 310.305, 21CFR314.80, 21CFR600.80, 21CFR1271, 21CFR 803.3.

C. Comments affecting Form 3500

None

D. **Comments affecting Form 3500A**

Comment: Action taken with drug can be added in section C.

FDA Response: FDA disagrees. This information equates to product use stopped or dose reduced, which is already captured on forms 3500 and 3500A.

Comment: We propose that the FDA require medical device adverse reporting use the MedDRA dictionary instead of the Patient Problem Codes. Rationale: Currently when reporting adverse events for medical devices, the current dictionary used is the "Patient Problem Codes of the Center for Devices and Radiological Health". This dictionary is much smaller (~800 terms) than the widely used MedDRA dictionary used when reporting adverse events with drugs (~20.6K terms). Using the MedDRA dictionary in place of the Patient Problem Codes would allow for more accurate recording of patient adverse events

FDA Response: FDA disagrees. FDA will continue to use Patient Problem Codes for medical devices instead of MedDRA coding. While the MedDra dictionary is able to adequately capture adverse events with drugs, patient problem codes and device problem codes are more effective at capturing device related adverse events.

Comment: Causality scale can be added in Section C.

FDA Response: FDA Disagrees. Causality is not assessed at the reporting level. Refer to 21 CFR 310.305(g), 21 CFR 314.80 (k), 21 CFR 600.80(k)(1), 21 CFR 803.16.

Comment: In section C10, Concomitant Medical Products and Therapy Dates (Exclude treatment of event), Dose of concomitant drugs should also be included.

FDA Response: FDA disagrees. Concomitant medical products are not limited to drug products, and may include medical devices, biologics and other regulated products. As concomitant products are not suspected to be related to the adverse event, it is not necessary to capture the dose.

Comment: In Section E1, along with Phone#, Email address can also be included.

FDA Response: FDA disagrees. Form 3500A section E already includes a field for email address, as does form 3500 Section G and form 3500B. However we have reviewed the name address field for Form 3500 and 3500A and believe data quality would be improved if separate fields for Last, name, first name, address,

state, zip code and Country were also included instead of one field labeled "name and address" to capture all of that information.

E. **Comments affecting Form 3500B**

Comment – One commenter urged the inclusion of a Spanish version of FDA form 3500B.

FDA Response: FDA agrees with the importance of communicating the benefits and risks of medical products to health care providers and patients, especially underrepresented populations, including those with Limited English proficiency. FDA's language access plan outlines some of the steps FDA is taking to improve communications with underrepresented populations. FDA's Drug safety communications are currently translated into Spanish and are available here. FDA is also working to improve the quality of the data received in adverse event reports received directly from consumers. At this time, FDA plans to focus resources on improving data quality from English-language consumer reports before evaluating how to best handle product experience information from non-English speaking consumers.

8b. Efforts at Consultation Outside the Agency

None

9. Explanation of Any Payment or Gift to Respondents

There is no remuneration, payment or gifts to any respondents to the Form FDA 3500, Form FDA 3500B [voluntary] or 3500A [mandatory]. Respondents to Form FDA 3500 and Form FDA 3500B receive a follow-up message by either email or standard mail to confirm their submission, acknowledge the processing of their information and thank them for their report.

10. Assurance of Confidentiality Provided to Respondents

Release of information submitted to FDA in voluntary adverse experience reports is governed by applicable law and regulations, including 21 CFR 20.111 and 21 CFR 20.63(f), which prohibits, with limited exceptions, FDA and a manufacturer in possession of such reports from releasing to the public the names and any information that would identify the voluntary reporter or any other person associated with an adverse event involving a human drug, biologic, or medical device product. Information that would identify the voluntary reporter or persons identified in the report name, address, institution, and any other information that would lead to the identities of the reporter or persons identified in the report, such as certain geographic information.

The voluntary version of the form used by health professionals to report directly to the FDA (Form FDA 3500) informs the reporter that their identity, including self-reporters, will be shared with the manufacturer of the product unless they indicate otherwise by checking box G5 on the form. The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise. This statement of confidentiality is provided as a prominent text display on the form itself, both paper and electronic in the section labeled, "Reporter Identification" and in the associated instructions.

To improve clarity, and to be consistent with Form 3500, FDA proposed to reword the confidentiality statement on Form 3500B that currently asks "May we give your name and contact information to the company that makes the product (manufacturer) to help them evaluate the product?" to "If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box" with a corresponding checkbox.

Additionally, the instructions for the 3500B state that "We ask only for the name and contact information of the person filling out the form in case we need more information. This information will not be given out to the public," and "Your name and contact information may be shared with the company that makes the product to help them better understand the problem you are reporting, unless you request otherwise." Thus, if a person checks the box in Section E, that person's name and contact information will not be released to a manufacturer.

11. Justification for Sensitive Questions

No questions of a private or sensitive nature are asked.

12. Estimates of Annualized Burden Hours and Costs

12 a. Annualized Hour Burden Estimate

The estimated annual reporting burden for this information collection is 909,395 hours.

- Form FDA 3500 = 14,383 hours
- Form FDA 3500B = 6,325 hours
- Form FDA 3500A = 888,687 hours

FDA estimates of the burden for completing the forms for this collection of information are noted in **Table 1**.

The time estimate for burden/response is based on input from clinicians and industry during form approval in the mid-1990's and then adjusted with a 10% increase in 2005 when some modifications were made to form content, primarily in Form FDA 3500A. The estimate for the 3500B is based on measurement of form completion time for mock reports by a number of non-healthcare professionals (consumers), using the final draft version of the consumer-friendly Form FDA 3500B. Based on the changes FDA proposed in Dec. 2014 the time to complete Forms 3500, 3500A and 3500B was adjusted to reflect a 10% increase.

Table 1 – Estimated Annual Reporting Burden

FDA Center/21 CFR section/FDA form	Number of respondents	Number of responses per respondent	Total annual response	Average burden per response	Total hours
Center for Biologics Evaluation and Research/Center for Drug Evaluation and Research					
Form 3500	14,727	1	14, 727	0.66 (40min)	9,720
Form 3500A(310.305, 314.80, 314.98, 600.80, 1271.350)	599	98	58, 702	1.21	71,029
Form 3500A (310.305 outsourcing facilities)	50	2	100	1.21	121
Center for Devices and Radiological Health					
Form 3500	5,233	1	5,233	0.66 (40min)	3,454
Form 3500A (803)	2277	296	673,992	1.21	815,530
Center for Food Safety and Applied Nutrition					
Form 3500	1,793	1	1,793	0.66 (40min)	1,183
Form 3500A	1,659	1	1,659	1.21	2,007
Center for Tobacco Products					
Form 3500	39	1	39	0.66 (40min)	26
All Centers					
Form 3500B	13,750	1	13,750	0.46 (30min)	6,325
Total					909,395

NOTE: CBER, Center for Biologic Evaluation and Research; CDER, Center for Drugs Evaluation and Research; CDRH, Center for Devices and Radiological Health; and CFSAN, Center for Food Safety and Applied Nutrition. FDA Form 3500 and FDA Form 3500B are for voluntary reporting; FDA Form 3500A is for mandatory reporting.

* The majority of the indirect, mandatory reports were not received by Agency on a paper version of form 3500A [by mail or fax] but via an electronic submission route.

12b. Annualized Cost Burden Estimate for Voluntary and Mandatory Reporters

The information collection costs imposed on voluntary reporters (healthcare professionals and patients/consumers) are as follows:

Approximately 34,200 reports from voluntary reporters, were submitted to FDA in CY2014 using the Form FDA 3500 and FDA 3500B from voluntary reporters. Each voluntary report is estimated to take 40 minutes when using the existing Form FDA 3500 and 30 minutes for the consumer-friendly Form FDA 3500B. Using 2014 Bureau of Labor Statistics data, the average hourly 'consumer' wage across all industries and all occupations was $45.42 including 100% overhead and an average hourly 'healthcare practitioner' wage was $73.08

including 100% overhead. Assuming that all reporters using the existing Form FDA 3500 will be HCPs and all reporters using the proposed consumer-friendly form (3500B) will be non-HCPs the annualized cost burden for those using the Form FDA 3500 will be about $1,051,000 and for those using the proposed Form FDA 3500B will be about $287,000, or **total voluntary reporting cost burden, $1,338,000**.

The information collection costs imposed on the user-facilities, and pharmaceutical, biological, medical device and dietary supplement industry are as follows:

Approximately 104,000 reports from pharmaceutical [drugs and biologics] manufacturers, and 784,000 device reports from user-facilities, importers or manufacturers, including follow-up reports, were submitted to FDA in CY2014 using the mandatory Form FDA 3500A. The number of mandatory dietary supplement reports for CY2014 was 2500. Each mandatory report requires 1.1 hour for data entry and review. This includes 36 minutes for a data entry keyer at a pay rate of $28.96per hour including 100% overhead and 30 minutes for a health practitioner at a pay rate of $73.08 per hour including 100% overhead for review. [Bureau of Labor Statistics May 2014; Occupational Employment Statistics, National Industry-Specific Occupational Employment and Wage Estimates - NAICS 325400 Pharmaceutical and Medicine Manufacturing]

Cost per response is estimated at 1.1 hours @ 36 minutes ($17.38) and 30 minutes ($36.54) or $53.92per report submitted]. Based on a total information collection burden of 888,000 responses for mandatory form 3500A, the **annual cost burden to user-facilities, and pharmaceutical, biological, device and dietary supplement industries would be about $47,877,000.**

13. Estimates of Other Total Annual Costs to Respondents and/or Record keepers/Capital Costs

There is no capital, start-up, operating or maintenance costs associated with this information collection. Those industry and other business respondents who are submitting mandatory reports to the Agency using Form FDA 3500A, expend capital for goods and services that support the ongoing internal functions of their business only as part of usual and customary business practices. The supplemental process for handling information transmitted to FDA has costs that are documented in section 12b, but there are no additional costs identified.

14. Annualized Cost to the Federal Government

The estimated cost to the Federal Government for forms FDA 3500, FDA 3500B and FDA 3500A is $12,267,000.

CENTER	Number of Reponses	Hours per Response	Total Cost
CBER/CDER	104,000	.6	Total contract reflected below
CDRH	784,000	.6	Total contract reflected below
CFSAN	2500	.6	Total contract reflected below
All Centers Voluntary Reports	34,200	.6	$1,317,000
Total			$12,267,000

(NOTE: CBER - Center for Biologic Evaluation and Research; CDER - Center for Drugs Evaluation and Research; CDRH - Center for Devices and Radiological Health; CFSAN – Center for Food Safety and Applied Nutrition)

104,000 pharmaceutical [drug and biologics] reports, 2500 dietary supplement reports, and 784,000 medical device reports can be expected to be submitted to FDA annually, via the mandatory reporting pathways. An additional 34,200 reports are submitted voluntarily to FDA's medical product centers.

CDER/CBER Contracts: Adverse event reporting data entry, MedDRA coding, and quality control ($5.281 million/year)
CDRH Contract: processing of medical device reports, including receipt of device reports by phone, coding, and data entry ($3.769 million/year)
CFSAN Contract: data entry and processing + maintenance of IT system ($1.9 million/year)

Reports processed by FDA staff require about 36 minutes for data entry and review. This includes 18 minutes for a GS-7/step 1 at a pay rate of $41.26 including 100% overhead per hour for the data entry and 18 minutes for a GS-13/step 1 at a pay rate of $ 87.04 including 100% overhead per hour for review. [From http://www.opm.gov/policy-data-oversight/pay-leave/salaries-wages/salary-tables/pdf/2015/DCB_h.pdf, 2015 Table]

15. Explanation for Program Changes or Adjustments

FDA is requesting a renewal with adjustments to the existing Forms FDA 3500, 3500A and 3500B.

In 2013, the Drug Quality and Security Act added new section 503B to the FD&C Act, under which a compounder may elect to become an outsourcing facility by registering with FDA. Outsourcing facilities are required to report adverse events to FDA in accordance with the content and format requirements established through guidance or regulation under § 310.305.

To facilitate implementation of this mandatory reporting requirement, changes were proposed to Form FDA 3500A. FDA published a Federal Register Notice on Feb. 19, 2015 which outlined for comment the burden estimate for adverse event reports submitted by human drug compounding outsourcing facilities. These estimates have been included in Table 1 above. In addition to mandatory reporting, many adverse events related to compounded drugs are reported voluntarily by healthcare professionals and consumers. Therefore, FDA is proposing changes to the voluntary versions of Forms FDA 3500 and 3500B to improve the ability to rapidly identify reports involving compounded drugs.

The existing Forms FDA 3500, 3500A and 3500B have proposed changes to each form, with respect to formatting, to enhance the clarity and utility of the information collected and to ensure the data can more easily be scanned by the automated Optical Character Recognition software at FDA. Several fields have been moved so that "like" data can be grouped in one place, thereby increasing the likelihood that reporters will fill-out this information.

Additionally, in several places, one field which was intended to capture several pieces of data has been split into several fields to improve the clarity of the data collected. The agency has estimated that these changes have increased the time taken to complete the forms by 10% and that increase is reflected in the estimated burden hours.

16. Plans for Tabulation and Publication and Project Time Schedule

The Agency has no plans for either tabulation or publication of this information collection.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

The Agency is not seeking approval to not display the expiration date of OMB approval.

18. **Exceptions to Certification for Paperwork Reduction Act Submissions**

There are no exceptions to the certification.