VISTAAR™

White Paper

Summary of FDA New PMS Guidance Under Section 522

www.vistaar.ai

Summary of FDA New PMS Guidance Under Section 522

Post-market surveillance (PMS) is an active, systematic, scientifically valid collection, analysis, and interpretation of data or other information about a marketed device. The data collected under a surveillance order help to address important public health questions on the safety and effectiveness of a device.

Section 522(a) (1) (A) of FD&C act specifies that the agency may issue a post-market surveillance order at the time of device approval or clearance or any time thereafter. Section 522 of FD&C act, 21 U.S.C. § 360l, authorizes FDA to require post-market surveillance in the following instances:

- Class II or class III device for which failure of device would be reasonably likely to have serious adverse health consequence, expected to have significant use in pediatric populations, intended to be implanted in the human body for more than one year and or intended to be a life-sustaining or life-supporting device used outside of a device user facility.

Section 402(j) (1) (A) (ii) of Public Health Service act (PHS act) (42 U.S.C. § 282(j) (1) (A) (ii)) also states that any "pediatric post-market surveillance required under section 522" which is considered to be an "applicable device clinical trial". As such, pediatric post-market surveillance must be in compliance with the registration and results submission requirements of section 402(j) of the PHS act (42 U.S.C. § 282(j)). Additional information on these requirements can be found at https://clinicaltrials.gov/. FDA intends to work with the manufacturer to help FDA determine the appropriate timeframe for a pediatric 522 post-market surveillance study.

Device issues appropriate for post-market surveillance may be identified through a variety of sources including analysis of adverse event reports, a recall or corrective action, post-approval data, review of premarket data, reports from other governmental authorities, or review of scientific literature. FDA may order post-market surveillance to:

- Better understand the nature, severity, or frequency of suspected problems reported in adverse event reports or in the published literature.
- Obtain more information on device performance associated with real-world clinical practice.
- Address long term or infrequent safety and effectiveness issues for implantable and other devices for which the premarket testing provided more limited information. For example, premarket evaluation of a device may be based on surrogate markers. Once the device is actually marketed, post-market surveillance may be appropriate to assess the effectiveness of the device in detecting or treating the disease or condition, rather than the surrogate. Data collected through post-market surveillance may include rates of malfunction or failure of a device intended for long-term use or incidents of latent sequelae resulting from device use.
- Better define the association between problems and devices when unexpected or unexplained serious adverse events occur after a device is marketed, if there is a change in the nature of serious adverse events (e.g., severity), or if there is an increase in the frequency of serious adverse events

The 522 order will specify device(s) subject to the surveillance order and the reason that requiring post-market surveillance (i.e., the public health question). A manufacturer must submit a post-market surveillance plan within 30 calendar days of receipt of 522 order. Per Section 522(b) (1) of the FD&C act and 21 CFR 822.17, FDA will review post-market surveillance plans and respond within 60 calendar days of receipt.

Table 1: The general content and format of a post-market surveillance submission

Items required	Circle Yes or No or N/A
21 CFR 822.9 – The submission must include:	
a) Organizational/administrative information	
(1) Name and address	**Yes or No or N/A**
(2) Generic and trade names of the device	**Yes or No or N/A**
(3) Name and address of the contact person for the submission	**Yes or No or N/A**
(4) Premarket application/submission number and device identifiers for the device	**Yes or No or N/A**
(5) Table of contents identifying page numbers for each section of the submission	**Yes or No or N/A**
(6) Description of the device (this may be incorporated by reference to the appropriate premarket application/submission)	**Yes or No or N/A**
(7) Product codes and list of all relevant model numbers	**Yes or No or N/A**
(8) Indications for use and claims for the device	**Yes or No or N/A**
21 CFR 822.10 – The surveillance plan must include:	
(a) The plan objective(s) addressing the surveillance questions identified in the 522 order	**Yes or No or N/A**
(b) The subject of the study, e.g., patients, the device, animals	**Yes or No or N/A**
(c) The variables and endpoints that will be used to answer the surveillance question, e.g., clinical parameters or outcomes	**Yes or No or N/A**
(d) The surveillance approach or methodology to be used	**Yes or No or N/A**
(e) Sample size and units of observation	**Yes or No or N/A**
(f) The investigator agreement, if applicable	**Yes or No or N/A**
(g) Sources of data, e.g., hospital records	**Yes or No or N/A**
(h) The data collection plan and forms	**Yes or No or N/A**
(i) The consent document, if applicable	**Yes or No or N/A**
Items required	**Circle Yes or No or N/A**
(j) Institutional review board information, if applicable	**Yes or No or N/A**
(k) The patient follow-up plan, if applicable	**Yes or No or N/A**
(l) The procedures for monitoring conduct and progress of the surveillance	**Yes or No or N/A**
(m) An estimate of the duration of surveillance, e.g., timeline for milestones	**Yes or No or N/A**
Items required	**Circle Yes or No or N/A**
(n) All data analysis and statistical test planned	**Yes or No or N/A**
(o) The content and timing of reports, e.g., reporting schedule	**Yes or No or N/A**

In addition to the items above, FDA also recommends post-market surveillance plan to include the following:

- An interim data release plan (include frequency of interim analyses, type of analysis, data endpoints that will be assessed, content (i.e., endpoints to be posted), and proposed frequency of posting on the FDA's 522 Post-market Surveillance Studies Database webpage).
- A background section (e.g., a brief description of the device, the regulatory history, the indications for use), and enrollment and recruitment plan

In general, section 522(b) (1) of FD&C act authorizes FDA to order prospective post-market surveillance for duration of up to 36 months. Further, under section 522(b) (2) of the FD&C act, FDA may by order require a prospective surveillance period of more than 36 months with respect to a device that is expected to have significant use in pediatric populations, if such period is necessary in order to assess the impact of the device on growth and development, or the effects of growth, development, activity level, or other factors on the safety or efficacy of the device. FDA may work interactively with the manufacturer to help FDA determine the appropriate time frame for a pediatric 522 post-market surveillance study.

FDA will evaluate the proposed surveillance plan to determine whether it is administratively complete and if the plan will result in the collection of useful data that can reveal unforeseen adverse events or other information necessary to protect the public health and will answer the surveillance question. FDA may issue one of the following letters; **Not Acceptable Letter, Approval Letter, Major Deficiency Letter and Disapproval Letter.**

However, if FDA is unable to complete the review of the post-market surveillance plan within 60 calendar days of issuance of a 522 order due to outstanding deficiencies that the manufacturer needs to address, intend for the post-market surveillance to be categorized as "Plan Overdue" on FDA's website. Failure of manufacturer to conduct post-market surveillance within timeframes under section 522 of FD&C act may result in enforcement action by FDA.

Changes to an approved post-market surveillance plan that FDA may consider to affect the nature or validity of the data collected could include changes to sample size, endpoints, follow-up assessments, etc.

When developing a surveillance plan, FDA and manufacturer should consider a least burdensome approach that is scientifically appropriate to address the surveillance question. If more than one post-market surveillance study is needed to address the post-market questions, each question is tracked as a unique requirement under the 522 order. Different types of post-market surveillance designs that could be used depending on the particular public health question include Randomized Clinical Trial, Prospective Cohort Study, Retrospective Cohort Study, Cross-Sectional Study, Enhanced Surveillance, Active Surveillance, Meta-Analysis, Prospective & Retrospective Study, Case Control Study, Non-Clinical Study, Animal Study and Other Design.

As per 21 CFR 822.38, manufacturers must submit interim and final reports as specified in the post-market surveillance plan. A 522 order can include the timing of reports. FDA recommends submitting two types of interim reports: "Enrollment Reports" and "Interim Post-market Surveillance Status Reports". An Enrollment Report provides progress towards the meeting enrollment milestones specified in the post-market surveillance plan. For Enrollment Reports, the timing can be based on the expected completion dates for those enrollment milestones. An interim Post-market Surveillance status report includes subject accountability as well as device performance data.

Unless alternative timeframes are specified in the 522 order, for each post-market surveillance requirement, manufacturers should submit an Interim Post-market Surveillance Status Report every 6 months for the first 2 years and annually. Thereafter, from the date of 522 post-market surveillance plan approval or other agreed-upon starting date, separately for each unique requirement. Manufacturers should continue this reporting schedule, for each unique requirement, until the Final Post-market Surveillance Report(s) are submitted. In accordance with the 522 order, the Final Post-market Surveillance Report should be submitted no later than three months after study/surveillance completion for a particular post-market surveillance requirement, which FDA considers to have occurred when the last data point is collected during the surveillance period (e.g., when the last subject completes the last follow-up visit).

FDA recommends all reports include a section that contains the following general information:

- Post-market surveillance tracking number (i.e., PS######)
- Manufacturer name and contact information (name of the individual or entity holding the approved PMA, or HDE, cleared 510(k), or De Novo order): Company Name/Institution Name, Street Address, City, State/Province, ZIP/Postal Code, Phone Number (include area code), Contact name and title, Contact e-mail address
- Date of issuance of the 522 order
- Date of post-market surveillance plan approval and, if applicable, dates of approval of any plan revisions
- Device trade name(s), subject to the 522 order
- Device model number(s), subject to the 522 order
- Report information: Date of the report, Description of the data included in the report, including: Enrollment data, Clinical study data, Non-clinical data (e.g., bench/laboratory), Animal45 study data and Other
- Type of submission: Enrollment Report, Interim Post-market Surveillance Status Report, Final Post-market Surveillance Report and Response to FDA correspondence for a deficient report or another reason (specify).

The Enrollment Reports, Interim Post-market Surveillance Status Report and Final Post-market Surveillance Report should include sufficient information to allow FDA and the manufacturer to track progress towards the enrollment milestones specified in the post-market surveillance plan, as detailed below Table 2.

Table 2: Type of information and content in Enrollment Reports, Interim Post-market Surveillance Status Report and Final Post-market Surveillance Report for FDA submission

Enrollment Reports	Interim Post-market Surveillance Status Report	Final Post-market Surveillance Report
• Begin and end dates of period covered by the report • Start and completion dates for clinical site(s) recruitment • Number of IRB approvals and number of clinical sites at which the surveillance was initiated • Subject-enrollment start date and expected completion date • Number of subjects enrolled (if applicable, this information should be presented for the entire subject population and for each subgroup, including sex, age, race, and ethnicity, as appropriate)	• Purpose of the post-market surveillance, including goals, objectives, and primary and secondary endpoints • Begin and end dates of period covered by the report • Date of database closure for the report (should not exceed three months prior to the submission of report) • if clinical study: Description of the patient population being studied, including: Specific illness or condition	• Purpose of the post-market surveillance, including goals, objectives, and primary and secondary endpoints • Begin and end dates of period covered by the final report • Date of database closure for the final report • if clinical study: Patient population being studied, including: Specific illness or condition Whether the post-market surveillance targets subpopulations (e.g., pediatric, geriatric), and targets for ensuring

• Comparison of target versus actual enrollment dates based on enrollment milestones specified in the post-market surveillance plan	Whether the post-market surveillance targets subpopulations (e.g., pediatric, geriatric), and targets for ensuring diversity with respect to sex, age, race, and ethnicity, as appropriate Total number of subjects to be studied Schedule of subject follow-up Subject accountability (e.g., enrolled, randomized, completed, withdrawn, lost to follow-up) at each follow-up time point for the entire population and broken down by subgroups, if applicable. To limit the potential bias in safety and effectiveness data, manufacturers should make every effort to reduce the number of subjects lost to follow-up • if applicable, an explanation for: delays in enrollment and plans to address challenges and meet enrollment milestones specified in the post-market surveillance plan subjects lost to follow-up, as well as any measure to minimize such future events subject and healthcare provider-initiated discontinuations Any deaths, including reports from post-mortem examinations • summary and interpretation of interim safety/effectiveness findings, as specified in the post-market surveillance plan • proposed interim summary data to be posted on FDA's 522 Post-market Surveillance Studies Database webpage	diversity with respect to sex, age, race, and ethnicity, as appropriate. Total number of subjects to be studied Schedule of subject follow-up Final accountability of enrolled subjects, compared to target Final accountability of number of subjects (e.g., enrolled, randomized, completed, withdrawn, lost to follow-up) at each follow-up time point, for the entire population and broken down by subgroups, if applicable If applicable, an explanation for: Subjects lost to follow-up, if known Subject and healthcare provider-initiated discontinuations Any deaths, including reports from post-mortem examinations Assessment of potential bias introduced by losses to follow-up (e.g., are subjects lost to follow-up different from those that remain under surveillance? Is the loss to follow-up differential by study group?) and impact on interpretation of results Summary and interpretation of final safety/effectiveness findings Proposed summary data to be posted on FDA's 522 Post-market Surveillance Studies Database webpage.

Upon receipt of an Interim or Final Post-market Surveillance Report, FDA determines your reporting status based on the schedule in the post-market surveillance plan. The reporting status categories are included: Report on Time, Report Overdue and Report Overdue/Received.

A manufacturer's progress status is considered based on current information available to the agency and may be revised accordingly based on the availability of new information. Each of these status categories are described as Plan Pending, Plan Overdue, Surveillance Pending, Ongoing, Delayed, Non-compliant, Completed, Terminated, Redesigned/Replaced, Hold and Consolidated.

Failure to commence surveillance within 15 months of a 522 order is prohibited act under section 301(q)(1)(C) of FD&C act, 21 U.S.C. § 331(q)(1)(C), and renders that the device misbranded under section 502(t)(3) of the FD&C act, 21 U.S.C. § 352(t)(3), failure to have an approved post-market surveillance plan or failure to conduct post-market surveillance in accordance with the approved plan will be the basis of enforcement action. There may be instances in which it is impossible or inappropriate for a manufacturer to complete a particular post-market surveillance order, and manufacturers may request exemption from the requirement to conduct post-market surveillance for their devices, which FDA will consider under 21 CFR 822.30.

After approval of manufacturer's plan, FDA may disclose the contents of original submission and any amendments, supplements, or reports, in accordance with applicable disclosure laws, such as the Freedom of Information act. When FDA discloses such information, FDA will continue to protect any trade secret or confidential commercial information, as well as any personal privacy information of patients.

****