Supplemental Information.

Survey 1:

Survey Questions:

1. Has your company identified any new valid safety signals from patient support programs, market research programs, or websites / social media from January 1, 2014 to December 31, 2016? Please refer to definitions at the bottom of the page.

2. If yes to #1, how many valid signals?

3. Did any valid safety signals become confirmed signals? Please refer to definitions at the bottom of the page.

4. If yes to #3, how many confirmed signals came from these sources (patient support programs, market research programs, or websites / social media)?

5. If yes to #3, could you have identified the signal through another source not listed above (e.g. from spontaneous sources)? Please respond 'yes' or 'no' and provide additional comments below.

6. If yes to #3, would you have identified the signal earlier through (1) patient support programs, market research programs, and web sites/social media (which ever apply) versus (2) spontaneous sources? Please elaborate below.

7. If yes to #3, was the signal initially identified through single case data review or aggregate analysis? Please elaborate below.

8. If yes to #3, what was the number of years since the product had been first marketed?

Survey 2:

Respond to the following questions based on valid or confirmed safety signals your company has identified from patient support programs, market research programs, and websites / social media from January 1, 2014 to December 31, 2016 (i.e. identified in Survey 1).

Survey Questions:

1. For **each valid** safety signal, which type of solicited program (patient support program, market research program, or websites / social media) did you first identify it? Please be as specific as possible, including type of PSP if applicable. Also, please provide a clear description of the program, including its design and type of information it was intended to collect or did collect.

2. For **each confirmed** safety signal, which type of solicited program (patient support program, market research program, or websites / social media) identified it? Please be as specific as possible, including type of PSP if applicable. Also, please provide a clear description of the program, including its design and type of information it was intended to collect or did collect.

3. Approximately for each valid signal, how much time was required to determine the validity of the identified signals to be confirmed or not? Please be as descriptive as possible.

4. For each unconfirmed valid signal, what were the reasons that each valid signal was not confirmed? Please be as descriptive as possible.

5. Did the valid or confirmed signal involve an event that was already labeled? If yes, please elaborate for each.

6. What was the total number of cases your company received from patient support programs between January 1, 2014 and December 31, 2016? For market research programs? For websites / social media?

Survey 3:

Respond to the following questions based on valid or confirmed safety signals your company has identified from patient support programs, market research programs, and websites / social media from January 1, 2014 to December 31, 2016 (i.e. identified in Survey 1).

Survey Questions:

1. Please provide a detailed description of the **purpose** of each program that has resulted in the identification of each of the valid and confirmed signals reported in Survey 1.

2. Please provide a detailed description of the signal detection **method** that identified each of the valid and confirmed signals (i.e. how was each signal identified, such as line listing review, disproportionality analyses in your company or external databases, signal identified by regulatory agency, signal identified through aggregate analyses of the specific program, other?).

3. Please provide a detailed description of the **nature** of each of the valid and confirmed signals (e.g., was the signal identifying serious or non-serious adverse events? If serious, why was it serious (important medical event, fatal, etc.)? Was the term already included in the core safety data sheet at the time of the identification of the signal?).

4. What **other information** can you share about each signal that you have not already provided (e.g., time of product on the market)?

Definitions:

Patient support program: An organized system where a marketing authorization holder receives and collects information relating to the use of its medicinal products. Examples are post-authorization patient support and disease management programs, surveys of patients and healthcare providers, information gathering on patient compliance, or compensation/re-imbursement schemes. [GVP Module VI.C.2.2.11]

Patient assistant programs: Any project with the aim of patient assistance in the form of compensation/reimbursement schemes which is solely charitable in design, without intent to collect information relating to the use of the medicinal product. PAPs may provide free or discounted medicines to people who meet specific guidelines. Note: PAPs that collect information relating to the use of the medicinal products involved are handled as PSPs for the purposes of safety data collection; some companies distinguish between Patient Support and Patient Assistance Programs.

Market research program: A market research program refers to the systematic collection, recording and analysis by a marketing authorization holder of data and findings about its medicinal products, relevant for marketing and business development. [GVP Module VI.C.2.2.11]

Websites / Social media: Web sites and applications that enable users to create and share content or to participate in social networking, such as Twitter, Facebook, LinkedIn, Pinterest, or Company websites that allow for user engagement.

Signal validation: The process of evaluating the data supporting a detected signal in order to verify that the available documentation contains sufficient evidence to justify further analysis of the signal. This evaluation should take into account the strength of the evidence, the clinical relevance and the previous awareness of the association. [GVP Module IX.A.1]

Signal confirmation: The process during which the competent authority of a Member State (where the signal concerns a medicinal product authorized in accordance with DIR), or the Rapporteur appointed by the Pharmacovigilance Risk Assessment Committee (PRAC) (where the signal concerns a product authorized in accordance with REG), decides whether or not a validated signal should be analyzed and prioritised by the PRAC. This should be done within 30 days from receipt of the validated signal. Signal confirmation is not intended to be a full assessment of the signal. The fact that a signal is confirmed does not imply that a causal relationship has been established, but that the signal should be discussed at EU level and further investigated by PRAC. [GVP Module IX.A.1]