DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear

The Food and Drug Administration's Center for Devices and Radiological Health (CDRH) is currently evaluating a potential postmarket safety issue associated with the use of syringe pumps. The potential safety concern is related to serious clinical consequences when delays in therapy, drug over-dose, drug under-dose, or lack of flow continuity occur while infusing at low rates. Serious adverse events have been reported relating to hemodynamic instability, loss of sedation, and increased pain in critically ill neonatal patients. This issue was brought to our attention through Medical Device Reports (MDRs), discussions with clinicians, and published literature[1].

Agency records indicate that your firm manufactures at least one syringe infusion pump. We are requesting your assistance in providing information about your experience with the issues described above. The information requested will help CDRH determine how to better evaluate, and if needed, mitigate these issues, while preserving the overall benefits that these types of devices provide. To assist FDA in this effort, please:

---

[1] Several literature articles were reviewed including, but not limited to:

Bartels K, Moss DR, Peterfreund RA, An analysis of drug delivery dynamics via a pediatric central venous infusion system: quantification of delays in achieving intended doses. *International Anesthesia Respiratory Society*, 2009; 109(4): 1156-1161.

Neff SB, Neff TA, Gerber S, Weiss MM, Flow rate, syringe size and architecture are critical to start-up performance of syringe pumps. *European Journal of Anesthesiology*, 2007; 24(7): 602-608.

Sherwin CMT, Medlicott NJ, Reith DM, Broadbent RS, Intravenous drug delivery in neonates: lessons learnt. *Archives of Disease in Childhood,* 2014; 99(6): 590–594.

Van der Eijk AC, van Rens R, Dankelman J, Smit BJ, A literature review on flow-rate variability in neonatal IV therapy. *Pediatric Anesthesia*, 2013; 23(1): 9-21.

1. Provide a summary of any analysis on actual causes, potential causes, or contributing factors (e.g., use considerations, patient conditions, concomitant and/or accessory device use, etc.) which may lead or contribute to a delay in therapy, under/over-dose, or lack of flow continuity when infusing at low rates for each model of syringe pump and relevant accessories. Additionally, please comment on the following:

    a. State the number of complaints that have been received over the past five years related to delay in therapy, under/over-dose, or lack of flow continuity when infusing at low rates. Note: please format your response data in a manner which stratifies complaints on an annual basis and includes the reported device brand name. The complaint listing should include complaints where the user may have expressed problems with hemodynamic stability or a decrease in the expected therapeutic effect of a medication (e.g., increase in pain, restlessness, unexpected changes in hemodynamic stability etc.) when starting and/or changing the programmed rate of an infusion. Comment on any changes in the volume of complaints and MDRs as well as contributing factors for complaints received.

    b. Provide an analysis of the complaints summarized within your response to question 1a, above. This analysis should include:

        - The age of the patients as well as the pediatric subgroup, if applicable (i.e., neonate, infant, child, or adolescent as defined in the Premarket Assessment of Pediatric Medical Devices Guidance for Industry and Food and Drug Administration Staff issued on March 24, 2014)
        - The rate of infusion
        - Type of medication infusing
        - The nature of the complaint (e.g., delay in therapy, under/over-dose, or lack of flow continuity)
        - Any relevant accessories which could have contributed to the described delay in therapy, under/over-dose, or lack of flow continuity (e.g., using a larger syringe, problems identified with setup or accessory devices, etc.)
        - Any analysis of the actual and potential contributing factors

    c. If applicable, describe the design features of the syringe pump and/or accessories which may mitigate the risk of delay in therapy, under/over-dose, or lack of flow continuity when infusion at low rates (e.g., alarms or alerts, use of smaller syringes, the placement of the syringe pump in relation to the patient, use of certain accessory devices, etc.).

    d. Describe any design change(s) or modification(s) to the device(s) or accessory devices, over the past five years that may be related to delay in therapy,

under/over-dose, or lack of flow continuity when infusing at low rates. Please include the date the design change(s) or modification(s) occurred.

e. Describe clinical scenarios that your firm is aware of where users have attempted to minimize effects from delay in therapy, under/over-dose, or lack of flow continuity when infusing at low rates (e.g., starting a second pump and letting it infuse for 30-60 minutes prior to connecting to a patient when changing infusion tubing, temporarily increasing the rate of infusion at startup and titrating the rate of infusion back to baseline after the patient has a therapeutic response, etc.).

f. If your investigation has proceeded to the point of making corrective or preventive actions, please summarize how you have verified or validated any changes to ensure that they are effective.

2. Comment on whether your device labeling (i.e., instructions for use) includes information pertaining to infusions at low rates.

   a. Identify the location of the relevant information (e.g., warnings, precautions, etc.) as well as the language where users are informed of steps to take to prevent delay in therapy, under/over-dose, or lack of flow continuity while infusing at low rates, and/or how to mitigate delay in therapy, under/over-dose, or lack of flow continuity at low rates, should it occur.

   b. If these steps are not included in the labeling, describe how users are expected to mitigate delay in therapy, under/over-dose, or lack of flow continuity while infusing at low rates. If applicable, describe how your firm makes this information clear to the device user (e.g., training).

3. Provide a summary of training provided to device users regarding infusions at low rates. Additionally, please:

   a. Describe any changes made in your training program regarding infusing at low rates for users over the past five years.

      i. If changes were made, please describe why you made those changes and comment on whether the changes were addressed in the labeling. If so, indicate the language used in the labeling as well as the relevant location (e.g., warnings, precautions, etc.).

   b. Provide copies of any written training materials you have related to infusing at low rates, including:
      i. Slides
      ii. Brochures or quick reference guides
      iii. Instructional videos

4. Quantify and provide rationale of what rates of infusion could result in delay in therapy, under/over-dose, or lack of flow continuity at startup or during changes (e.g., titrating

the rate of an infusion, changing a syringe and/or infusion tubing, pausing and restarting the pump) to the rate of an infusion?

5. For each type of syringe pump manufactured by your firm, please:

    a. Quantify the lowest rate of infusion the syringe pump can be programmed to administer.

    b. Provide a statement of accuracy requirements for the lowest rate of infusion the syringe pump can be programmed to administer.

6. Describe the performance testing your firm has conducted to verify infusion accuracy at the lowest programmable rates. Additionally, please:

    a. Provide a summary of the test protocol and test results.

    b. Summarize any testing completed to evaluate the effects of the infusion system using accessory devices (e.g., different infusion tubing, different sizes and brands of syringes, etc.).

Please submit a written response via email by November 18, 2014 to CDRHSignalManagement@fda.hhs.gov and Kathleen.White@fda.hhs.gov. Please include your manufacturer and device name in the subject line of the email.

If you have any questions concerning this letter, please contact Kathleen White, BSN, RN, MBA, at the above email address or by telephone at 301-796-5832.

Sincerely,

Aron Yustein, M.D.
Deputy Director and Chief Medical Officer
Office of Surveillance and Biometrics
Center for Devices and Radiological Health